Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses

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ABSTRACT

Background: Extensive literature suggests an association between general pesticide use and Parkinson's disease (PD). However, with few exceptions, little is known about associations between specific pesticides and PD.
Objective: We evaluated use of pesticides and incident PD in 38,274 pesticide applicators and 27,836 of their spouses in the Agricultural Health Study cohort followed over 20 years.
Methods: We used self-reported information on ever-use of 50 specific pesticides as of enrollment for both applicators and spouses, and considered intensity-weighted lifetime days (IWLD) reported at enrollment and through the first 5-year follow-up among applicators. We estimated covariate-adjusted hazard ratios (HR) and 95% confidence intervals (CI) using Cox regression. We also examined heterogeneity in associations by history of head injury and chemical resistant glove use.
Results: A total of 373 applicators and 118 spouses self-reported incident doctor-diagnosed PD. Ever-use of the insecticide terbufos (HR:1.31, 95%CI:1.02–1.68) and the herbicides trifluralin (HR:1.29, 95%CI: 0.99–1.70) and 2,4,5-T (HR:1.57, 95%CI:1.21–2.04) was associated with elevated PD risk. On the other hand, diazinon (HR:0.73, 95%CI: 0.58–0.94) and 2,4,5-TP (HR:0.39, 95%CI:0.25–0.62) were associated with reduced risk. We observed heterogeneity in ever-use associations by head injury and chemical-resistant glove use for some pesticides, with higher risk among those who reported a history of head injury, or who did not use gloves. PD risk was also elevated for applicators in the highest category of IWLD for dichlorvos, permethrin (animal use), and benomyl.
Conclusions: We found evidence of increased PD risk for some pesticides. Our results also suggest higher susceptibility for pesticide-associated PD among individuals with head injury as well as protection with use of chemical resistant gloves, although further research is needed to understand the impact of head injury. Research on current and newer pesticides, including mechanisms relevant to PD, is important given widespread pesticide use.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting around 1–2% of adults over the age of 65 years (Hirtz et al., 2007). PD is associated with substantial economic burden (Kowal et al., 2013) which is likely to increase with the aging of the population (US Administration on Aging, 2012). Many pesticides are neurotoxic, and some epidemiologic studies have linked general pesticide use with PD (Goldman et al., 2017; Pezzoli and Cereda, 2013; van der Mark et al., 2012). Although most of these studies evaluated functional (i.e., fungicides, insecticides, and herbicides) or chemical (i.e., organochlorine or organophosphate insecticides) classes, rather than

individual pesticides, some evidence from human and toxicological studies points to associations of PD with the insecticides dieldrin and rotenone and with the herbicides 2,4-dichlorophenoxyacetic acid (2, 4-D) and paraquat (Goldman et al., 2017; Kanthasamy et al., 2005; Tanner et al. 2009, 2011; Weisskopf et al., 2010). Given that some of these and other pesticides continue to be widely used, with annual usage of all pesticides totaling over one billion pounds in the United States (US) alone (Atwood and Paisley-Jones, 2017), identifying links between specific pesticides and PD can have important implications.

The Agricultural Health Study (AHS) is a prospective cohort study of farming populations from North Carolina and Iowa (Alavanja et al., 1996), with follow-up ongoing for over 20 years. Two previous investigations on pesticides and PD were conducted in the AHS. The first included data from the full cohort and examined pesticide exposure data collected at enrollment in relation to self-reported PD through the first study follow-up, approximately 5 years later (Kamel et al., 2007). The second effort, the Farming and Movement Evaluation (FAME) study, was a case-control study nested within the cohort, which assessed PD cases through the first follow-up, but with self-reported PD confirmed by in-person assessment by movement disorder specialists and with collection of additional exposure data for specific pesticides (identified *a priori*) including some not well covered in the original AHS surveys (Tanner et al., 2011). Since then, self-reported incident PD was ascertained in two additional follow-up surveys. A recent update of mortality in the AHS found that pesticide applicators experience higher than expected mortality from PD than the general populations of Iowa and North Carolina, indirectly implicating farming exposures including pesticides (Shrestha et al., 2019a). Therefore, with additional PD cases identified from extended follow-up as well as updated exposure data, we examined associations between individual pesticides and incident PD that occurred over 20 years of follow-up among private pesticide applicators and their spouses.

2. Material and methods

2.1. Study population

The AHS is described in detail elsewhere (Alavanja et al., 1996). In 1993–1997 (Phase 1), 52,394 private pesticide applicators (97.4% male, mainly farmers) completed an enrollment questionnaire at pesticide licensing locations (see Supplemental Fig. 1 for study timeline). A take-home questionnaire requesting additional pesticide use information, was completed by 22,916 (44% of those who enrolled). Applicators were also given a questionnaire to be filled out by their spouses; 32,345 spouses (75% of married spouses, 99.3% female) enrolled in the study. Enrollment questionnaires were self-administered. Computer-assisted follow-up telephone interviews were conducted in 1999–2003 (Phase 2) and 2005–2010 (Phase 3). Participants completed either self-administered mailed questionnaires or computer-assisted telephone interviews in 2013–2016 (Phase 4). Questionnaires can be found at https://aghealth.nih.gov/collaboration/questionnaires.html. The Phase 2 survey was completed by 33,456 applicators and 23,796 spouses, Phase 3 by 24,170 applicators and 19,959 spouses, and Phase 4 by 24,145 applicators and 18,186 spouses. The institutional review boards of the National Institute of Environmental Health Sciences and the National Cancer Institute approved the study.

2.2. Pesticide use

The applicator enrollment questionnaire asked about ever-use of 50 pesticides, and duration and frequency of use for 22 specific pesticides. The applicator take-home questionnaire asked participants to provide duration and frequency of use for the remaining 28 pesticides, and to complete a checklist of ever-use of additional specific pesticides ("other pesticides used") that were not covered in the enrollment questionnaire. Our current analysis focuses on the 50 pesticides for which detailed

information on duration and frequency of use were collected either in the enrollment or the take-home questionnaire (although other pesticides were considered in some analyses as noted). These questionnaires also sought detailed information on pesticide use practices including application methods, mixing processes, personal protective equipment use, and other workplace hygiene factors. The enrollment questionnaire asked applicators what type of personal protective equipment they generally wore when they personally handled pesticides, including respirator/gas mask, fabric/leather gloves, and chemical-resistant gloves. The enrollment spouse questionnaire only asked about ever-use of the 50 specific pesticides. All participants were asked about their overall use of any pesticides, including years and days personally mixed or applied pesticides.

We also used pesticide information collected at Phase 2 (conducted 2–10 years after enrollment, 5 years on average). At this interview, applicators and spouses were asked to provide the names and number of days of use of specific pesticides in the year prior to the interview (or most recent year used) and information on pesticide use practices. Although the Phase 2 interview asked only about pesticide use in the most recent year, when estimating cumulative exposure, we assumed that year represented pesticide use during the period since the Phase 1 exposure assessment.

We used several approaches to characterize pesticide exposures. First, we examined ever-use of the 50 specific pesticides. Exposure intensity weights were previously derived using an algorithm that incorporates information on mixing practices, application methods, repair status, and personal protective equipment use (Coble et al., 2011). We then used intensity-weighted lifetime days (IWLD) of pesticide use (i.e., the product of years of use and days used per year weighted by exposure intensity) as a measure of cumulative exposure for applicators. IWLD days were categorized using cut-points based on the exposure distribution of the full sample and number of PD cases (i.e., at least five cases) in each exposure category. Specifically, we created a four-category exposure variable (never use and three categories among users with cut-points at tertiles of IWLD). When sample size was limited, we created a three-category variable by cutting at the median of IWLD. As only applicators were asked about duration and frequency of use of specific pesticides in Phase 1, the IWLD analyses were limited to the applicators. We further restricted these analyses to male applicators due to the small number of female applicators.

In addition to examining individual pesticides, we created two ever-use pesticide groups based on potential mechanisms implicated in PD pathogenesis. The first group included use of any pesticides linked to mitochondrial complex I inhibition (namely, benomyl, permethrin, rotenone, dichlorvos, and thiabendazole) (Binukumar et al., 2010; Tanner et al., 2011); the second group included pesticides linked to aldehyde dehydrogenase inhibition (namely, benomyl, captan, folpet, aldrin, dieldrin, mancozeb/maneb, ferbam, thiram and ziram) (Fitzmaurice et al., 2013, 2014). Some pesticides of interest, including rotenone, thiabendazole, folpet, ferbam, and thiram, were not among the 50 main pesticides queried at enrollment and were only asked of applicators (not spouses) on the checklist of "other pesticides used" in the Phase 1 take home questionnaire. Although both applicators and spouses could have reported their use in the Phase 2 open-ended survey, we considered only Phase 1 exposures for these analyses to maximize the analytical sample with complete information on these pesticides and for analytical simplicity. To accommodate the fact that not all participants provided data and only a portion completed the take-home questionnaire, we conducted analyses (that focused on Phase 1 exposures only) in two different analytical subsets. We first considered only those participants with complete data on all individual pesticides in a group (so, the analysis was limited to the male applicators who returned the take-home questionnaire). In a secondary analysis in the overall sample, we considered participants as exposed if they indicated they used *at least one* of the pesticides in the group, regardless of missing information on other pesticides in that group.

2.3. Parkinson's disease

Potential PD cases were identified by self-report in all AHS surveys (i. e., positive response to "has a doctor ever told you that you had been diagnosed with Parkinson's disease?"), as well as via linkage to the National Death Index and state death registries (with PD recorded as an underlying or contributing cause of death). Self-reported PD cases identified through Phase 2 were previously confirmed by movement disorder specialists as a part of the FAME study, via structured clinical examinations and medical records; self-reported PD was confirmed in 84% (Tanner et al., 2011). Between 2012 and 2017 (around and following the Phase 4 survey), we attempted to validate all potential PD cases (prevalent as well as incident), including those considered PD cases in FAME (n = 810). Briefly, each participant with potential PD, or their proxy (if deceased or too ill), was asked to complete a detailed screening questionnaire on PD diagnosis, symptoms, characteristics, and treatment. We also requested consent to obtain medical records from their treating or diagnosing physician. Screeners were obtained for 510 prevalent and incident cases. The PD screeners were evaluated by a movement disorder specialist to adjudicate PD status using criteria analogous to clinical diagnostic criteria proposed by Gelb et al. (1999). This evaluation classified 75% as probable or possible PD, 11% as questionable or other neurological disorders, and 14% as not having PD. Among those for whom medical records were obtained (n = 65), 91% were confirmed as PD by medical records and 9% were considered questionable (because of conflicting information from multiple physicians and/or physician's reporting of inadequate evidence to distinguish from other neurological disorders).

After excluding self-reported prevalent cases (age at diagnosis ≤ age at enrollment) and those with no information on age at diagnosis, we had 598 eligible incident potential cases (440 with and 158 without screener data; Supplemental Fig. 2). We excluded cases without supporting PD symptoms or medications (99 of 440 participants screened) and those who did not provide consistent responses across surveys (8 of the 158 without screener information), leaving 491 cases for analysis. Overall, 80.6% of the 491 cases had some confirmatory information from a validation screener, medical record, FAME evaluation, or death certificate. We used the age at diagnosis provided at the earliest survey in which age at diagnosis was reported.

2.4. Study sample

Participants eligible for our analysis included a total of 38,798 applicators and 28,238 spouses who completed at least one follow-up survey or the PD validation screening questionnaire (Fig. 1). After excluding prevalent cases, those with inconsistent PD information across surveys, or those lacking other supporting information, we had 38,274 applicators and 27,836 spouses for ever-use of pesticides analyses (n = 66,110; 491 with PD). For IWLD analyses of the 22 pesticides for which frequency and duration of use were asked in the enrollment questionnaire, the final sample size included 37,284 male applicators (372 PD cases) and for the 28 pesticides for which frequency and duration of use were asked in the take-home questionnaire, the final sample size included 19,068 male applicators (237 PD cases).

2.5. Statistical analysis

2.5.1. Pesticide use at enrollment

We first examined bivariate relations of incident PD with baseline covariates that included applicator status, sex, state of residence, cigarette smoking, alcohol consumption, and education. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for associations between pesticide use reported at enrollment and incident PD. We used attained age as the time scale with left truncation at enrollment and always adjusted for sex, state of residence, smoking status, and education. Models for individual pesticides were additionally adjusted for the top four pesticides among those whose Spearman correlation with the pesticide of interest was 0.40 or greater. Whenever the proportional hazards assumption failed for a pesticide (p-value for interaction between age and pesticide ≤ 0.10), we allowed hazards to vary by the median age (63 years). Ever-use analyses were conducted in a combined sample of applicators and spouses, and separately for male applicators (n = 37,284) and female spouses (n = 27,673) (female applicators and male spouses, respectively, were excluded from these analyses due to small numbers). In the IWLD analyses among male applicators, we conducted a test for trend using the median value for each exposure category as an ordinal variable in regression models.

Information on smoking (n = 691) and education (n = 2474) was missing for some participants, and further, some participants reported 'something else' for education (n = 2625). We treated 'something else'
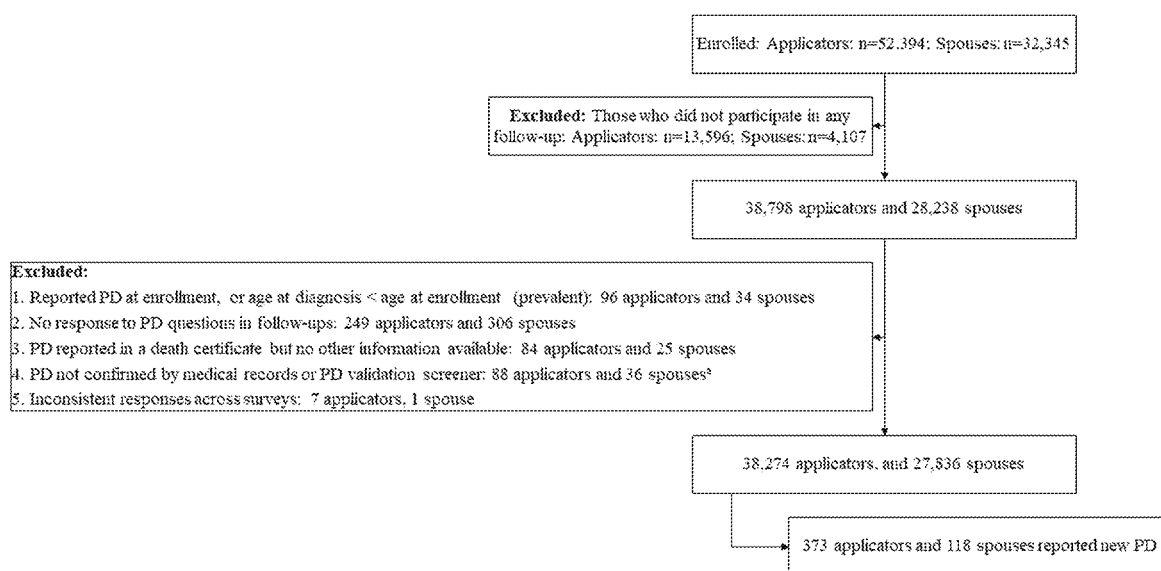

Fig. 1. Sample selection for pesticide and Parkinson's disease (PD) analysis in the Agricultural Health Study. [a]includes n = 2 spouses selected for validation based on FAME screening who did not report PD.

as a missing covariate and used multiple imputation to impute missing covariates (i.e., education and smoking). We created five imputed datasets, performed regression analysis in each dataset, and combined those results to estimate parameters and their standard errors using SAS PROC MIANALYZE (SAS Institute Inc, 2015).

Wearing chemical-resistant gloves was previously shown to modify PD associations with some pesticides (Furlong et al., 2015). Further, individuals with head injury may be more susceptible to pesticide-associated PD risk – the underlying hypothesis being combinations of risk factors acting in concert increase disease vulnerability (the "multiple-hit hypothesis") (Lee et al., 2012). We examined potential heterogeneity in the associations of PD with ever-use of pesticides by these characteristics (by testing for the interaction between pesticides and these characteristics), when each cross-classified category of exposure and factor contained at least five cases. Applicators were asked about a history of head injury requiring medical attention only in the take-home questionnaire, whereas all spouses were asked about head injury, and thus heterogeneity by head injury was evaluated in a smaller subset (19,222 applicators and 26,666 spouses resulting in a total of 45,888 participants). Only applicators (in the enrollment questionnaire) but not spouses were asked about chemical resistant glove use and thus heterogeneity by chemical resistant glove use was evaluated in male applicators only (n = 32,816). We also stratified the analysis by follow-up time ($\leq$10 years and >10 years) for ever-use analysis. Potential heterogeneity was not examined for IWLD due to limited sample size.

To examine the potential impact of loss-to-follow up, we performed a sensitivity analysis using inverse probability of censoring weights (Howe et al., 2016). Briefly, we used weighted Cox models to estimate HRs and 95% CIs, adjusting for covariates and using stabilized inverse probability weights. For stabilized weight estimation, first we transformed our data from a single record per person into person-year data (i.e., with multiple records per person). Then, we used logistic regression analyses to calculate the denominator of the weights, or probability of overall participation in Phase 4 conditional on exposure, year and baseline covariates (age, sex, education, smoking, alcohol use, state of residence; missing values imputed for covariates whenever applicable), as well as to calculate the numerator of the weights, or probability of overall participation in Phase 4 conditional only on year. We estimated stabilized weights as the ratio of cumulative conditional probabilities.

Lastly, we used logistic regression to analyze two other groups of cases (i) all "confirmed" prevalent and incident PD cases (n = 66,216 with 597 PD cases), and (ii) all "potential" prevalent and incident PD cases (any self-reported cases or reported on death certificates) (n = 84,739, with 860 PD cases). Statistical significance was determined using two-sided tests with α of 0.05. We performed statistical analyses using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

2.5.2. Pesticide use through Phase 2

We also examined associations between cumulative pesticide use through Phase 2 and incident PD. However, given the lower exposure and outcome prevalence in spouses, we performed this analysis only in male applicators. About 14% of the applicators included in our analysis were missing Phase 2 exposure data due to Phase 2 non-response. To account for the missing exposure data due to non-response, we used a multiple imputation approach developed specifically for AHS applicators (Heltshe et al., 2012). This approach used information on several factors including demographics, farm characteristics, prior pesticide use, and medical conditions that predicted missingness to impute use of specific pesticides for the Phase 2 non-responders. We created five imputed datasets which were then converted to person-year datasets allowing pesticide exposure information (ever-use and IWLDs) through Phase 2 to vary until their time at risk. We applied a Cox model applied to each imputed dataset and combined those results to obtain an HR and 95% CI using SAS PROC MIANALYZE (SAS Institute Inc, 2015). This analysis was limited to the previously described 50 specific pesticides.

Information on smoking and education was missing for only 1% and 4% of the sample, and we used a missing indicator category for this analysis.

3. Results

Characteristics of participants at enrollment differed by PD status (Table 1). Older participants, applicators, males, and those from North Carolina were more likely to develop PD, while current smokers and alcohol drinkers were less likely to develop PD. Chemical resistant glove use and a history of head injury requiring medical attention were similar between the two groups, although when adjusted for age, sex, state, education, and smoking status, we found an inverse association between having a head injury and incident PD (HR: 0.71, 95% CI: 0.46, 1.09).

3.1. Phase 1 pesticides

In the analysis examining lifetime days of *any* pesticide use in relation to incident PD in the overall sample, we generally observed positive HRs for higher lifetime days compared to never use, although we did not see a monotonic increasing trend (for example, HRs for the third and the fourth quartiles compared to never use were 1.27 (95% CI: 0.82, 1.98) and 1.07 (95% CI: 0.69, 1.67), respectively, Supplemental Table 1). In the female spouses only analysis, we observed increased risk (HR: 1.58,

Table 1
Characteristics of Agricultural Health Study participants at enrollment (n = 66,110).

Characteristics	No PD (n (%))[a] (n = 65,619)	Incident PD (n (%))[a] (n = 491)
Age (years)		
$\leq$45	31,843 (48)	53 (11)
46–55	16,479 (25)	109 (22)
56–65	12,382 (19)	206 (42)
>65	4915 (7)	123 (25)
Participant		
Spouse	27,718 (42)	118 (24)
Applicator	37,901 (58)	373 (76)
Sex		
Female	28,546 (44)	117 (24)
Male	37,073 (56)	374 (76)
State of residence		
Iowa	43,319 (66)	299 (61)
North Carolina	22,300 (34)	192 (39)
Education[b]		
$\leq$ High school graduate	31,301 (50)	300 (64)
1–3 years beyond high school	16,507 (26)	94 (20)
College graduate or more	12,732 (20)	77 (16)
Something else	2624 (4)	1 (0)
Smoking status[c]		
Never smoker	40,305 (62)	296 (61)
Former smoker	16,573 (26)	159 (33)
Current smoker	8056 (12)	30 (6)
Alcohol consumption (past 12 months)[d]		
No	23,979 (38)	221 (49)
Yes	38,420 (62)	230 (51)
Chemical resistant glove use[e]		
No	6193 (19)	65 (20)
Yes	26,299 (81)	259 (80)
Head injury requiring medical attention[f]		
No	41,911 (92)	316 (93)
Yes	3638 (8)	23 (7)

[a] % may not add to 100% due to rounding.
[b] Education missing for n = 2474.
[c] Smoking status missing for n = 691.
[d] Alcohol consumption missing for n = 3260.
[e] Chemical resistant glove use information was not sought from spouses and missing for n = 5458 applicators.
[f] Applicators provided information on head injury only in the take-home questionnaire.

95% CI: 1.00, 2.50) in those exposed to more than the median days as compared to never use. In the male applicators only analysis, associations for higher quartiles of lifetime days compared to the lowest quartile were slightly inverse. In a combined analysis of applicators and spouses (Table 2), we found positive associations for the organophosphate insecticide terbufos (HR:1.30, 95% CI: 1.02, 1.68) and the herbicides trifluralin (HR:1.29, 95% CI: 0.99, 1.70) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) (HR:1.57, 95% CI: 1.21, 2.04), and inverse associations for ever-use of the organophosphate insecticide diazinon (HR: 0.73, 95% CI: 0.58, 0.94), the fumigant ethylene dibromide (HR: 0.35, 95% CI: 0.14, 0.84), and the herbicide 2,4,5-TP [2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid] (HR: 0.39, 95% CI: 0.25, 0.62). These associations remained when analyses were performed separately for male applicators (Supplemental Table 2). Separate analyses for female spouses (Supplemental Table 2) were limited to only a few pesticides due to fewer PD cases; elevated (HR > 1.40), yet imprecise, risk was observed for the herbicides glyphosate, trifluralin, and cyanazine.

We found heterogeneity in associations for ever-use of some pesticides and PD risk by head injury (Table 3). We found higher PD risk for the three organochlorine insecticides chlordane, dichlorodiphenyltrichloroethane (DDT), and toxaphene, the two organophosphate insecticides diazinon and phorate, the insecticide permethrin (animal and crop use combined), the fumigant methyl bromide, and the herbicides paraquat and pendimethalin among those who reported a history of head injury as compared to reduced or null associations among those did not report a history of head injury (p for heterogeneity ≤0.10). For example, the HR for paraquat among those with a history of head injury was 3.20 (95%CI: 1.38, 7.45) versus 1.00 (95%CI: 0.71, 1.41) for those without a history (p for heterogeneity = 0.01).

Similarly, we found that five herbicides (dicamba, imazethapyr, metolachlor, trifluralin, and metribuzin) were associated with elevated PD risk among those who did not use chemical-resistant gloves as compared to reduced or null associations among glove users, although directions were reverse for metalaxyl (Table 3). In the analyses stratified by follow-up time (≤10 years and >10 years), we found that HRs for some herbicides including alachlor, butylate, chlorimuron ethyl, trifluralin, 2,4-D, and atrazine were elevated for the first 10 years of follow-up, but not for later years (Supplemental Table 3).

In the analyses examining IWLD through Phase 1 in male applicators (Table 4), we saw no clear monotonic exposure-response for pesticides associated with elevated PD risk. There were a few suggestive patterns. Specifically, we saw elevated HRs for individuals in the highest category of IWLD of the insecticides dichlorvos [HR:1.46 (95% CI: 0.98, 2.19), p-trend:0.06] and permethrin (animal use)[HR:1.44 (95% CI: 0.85, 2.44), p-trend: 0.21], and the fungicides benomyl (HR: 1.34 (95% CI: 0.64, 2.80), p-trend:0.31], captan [(HR: 1.27 (95% CI: 0.74, 2.20), p-trend:0.36], and chlorothalonil [HR: 1.29 (95% CI: 0.66, 2.56), p-trend:0.41] as compared to those who never used those pesticides, although risk estimates were very imprecise as reflected by the wide confidence intervals. For the herbicides terbufos and trifluralin (for which we observed significant positive association in the ever-use analysis), HRs were generally elevated for all tertiles as compared to never use. For heptachlor, HRs were higher for the two lower tertiles than for the upper. HRs in the higher tertiles of the insecticides aldrin, toxaphene, carbaryl, diazinon, and malathion were lower than in the never use category. The results (odds ratio estimates) were similar when we included "confirmed" prevalent cases (Supplemental Tables 4 and 5), or any "potential" PD cases (data not shown). The HR estimates using inverse probability weights were also similar (Supplemental Table 6).

In the male applicators returning take-home questionnaires, none of the pesticide groups – mitochondrial complex I inhibitors [HR: 0.96 (95%CI: 0.71, 1.29)] or aldehyde dehydrogenase inhibitors [(HR: 0.84 (95%CI: 0.65, 1.11)] – were associated with increased PD risk, although we observed heterogeneity by head injury for ever-use of mitochondrial complex I inhibitors with higher HR among those who experienced head injury [HR: 2.42 (95%CI: 0.91, 6.47)] vs reduced HR among those

Table 2

Ever-use of pesticide reported at enrollment and Parkinson's disease (PD) risk in all participants (n = 66,110).

Pesticide	No PD, n (%)[a]	PD, n (%)[b]	HR (95% CI)[c]
Organochlorine insecticide			
Aldrin	6507 (11.1)	98 (23.7)	0.91 (0.68, 1.23)
Chlordane	9758 (16.5)	125 (29.8)	1.05 (0.82, 1.34)
Dieldrin	2440 (4.1)	38 (9.2)	0.88 (0.60, 1.30)
DDT	8954 (15.4)	143 (34.8)	0.86 (0.67, 1.12)
Heptachlor	5442 (9.4)	87 (21.3)	1.01 (0.74, 1.38)
Toxaphene	5160 (8.7)	59 (14.1)	0.80 (0.60, 1.08)
Lindane	7250 (12.1)	74 (17.7)	0.92 (0.71, 1.19)
Carbamate insecticide			
Aldicarb	3809 (6.5)	28 (6.9)	1.05 (0.68, 1.62)
Carbaryl	27,180 (45.5)	231 (55.4)	1.09 (0.87, 1.37)
Carbofuran	10,017 (16.7)	110 (26.6)	0.95 (0.74, 1.21)
Organophosphate insecticide			
Chlorpyrifos	16,700 (26.8)	143 (30.7)	0.92 (0.74, 1.13)
Coumaphos	3423 (5.7)	35 (8.4)	1.04 (0.73, 1.47)
Diazinon	13,979 (23.3)	105 (25.1)	0.73 (0.58, 0.94)
Dichlorvos	4425 (7.3)	48 (11.5)	1.12 (0.83, 1.53)
Fonofos	8219 (13.6)	75 (17.7)	0.91 (0.70, 1.19)
Malathion	28,496 (48.7)	253 (62.6)	1.01 (0.78, 1.30)
Parathion	5661 (9.5)	62 (14.8)	0.98 (0.74, 1.30)
Phorate (≤63 y)[d]	5618 (18)	39 (36.1)	1.33 (0.85, 2.08)
>63 y	5786 (22.1)	73 (26.1)	0.71 (0.52, 0.97)
Terbufos	13,718 (23.8)	138 (35.4)	1.30 (1.02, 1.68)
Permethrin insecticide			
Permethrin (Crops)	5263 (8.8)	36 (8.8)	0.99 (0.70, 1.40)
Permethrin (Animals)	5696 (9.4)	41 (9.8)	1.07 (0.77, 1.48)
Fumigant			
Carbon disulfide/Carbon tetrachloride	2099 (3.5)	31 (7.3)	1.03 (0.71, 1.50)
Aluminum phosphide	1707 (2.8)	16 (3.8)	1.08 (0.65, 1.78)
Ethylene dibromide	1294 (2.2)	5 (1.2)	0.35 (0.14, 0.84)
Methyl bromide	5707 (9.5)	46 (10.8)	0.86 (0.59, 1.25)
Fungicide			
Benomyl[e]	*3492 (6)*	*26 (6.4)*	*0.80 (0.48, 1.31)*
Benomyl (≤ 63y)[d,e]	*1664 (5.3)*	*4 (3.6)*	*0.35 (0.11, 1.10)*
> 63y	*1828 (6.8)*	*22 (7.5)*	*0.99 (0.58, 1.68)*
Captan	4617 (7.7)	33 (8)	0.84 (0.59, 1.20)
Chlorothalonil	2899 (4.8)	21 (5)	0.97 (0.59, 1.60)
Maneb (≤63 y)[d]	1685 (5.2)	8 (7)	1.43 (0.63, 3.22)
>63 y	2030 (7.3)	21 (7)	0.75 (0.44, 1.25)
Metalaxyl	7968 (13.6)	58 (14.3)	0.85 (0.61, 1.18)
Herbicide			
Alachlor	19,057 (32.1)	187 (45.6)	1.13 (0.88, 1.45)
Butylate (≤63 y)[d]	5750 (18.3)	38 (34.9)	1.31 (0.86, 2.01)
>63 y	5245 (19.7)	65 (23.4)	0.87 (0.64, 1.20)
Chlorimuron ethyl	12,693 (21.8)	101 (25.6)	1.04 (0.80, 1.36)
Dicamba	17,945 (31)	161 (41.2)	0.94 (0.72, 1.22)
EPTC	7049 (12.2)	54 (14.1)	0.84 (0.61, 1.15)
Glyphosate	35,406 (58.6)	291 (67.4)	1.10 (0.87, 1.39)
Imazethapyr	15,124 (26.3)	126 (32.6)	1.04 (0.79, 1.37)
Metolachlor	16,114 (27.9)	127 (32.6)	0.80 (0.62, 1.03)
Paraquat	8526 (14.2)	87 (20.4)	1.09 (0.84, 1.41)
Pendimethalin	15,250 (26.1)	127 (31.9)	1.07 (0.83, 1.37)
Petroleum distillate	16,756 (28.9)	146 (37)	0.93 (0.73, 1.18)
Trifluralin	18,665 (32.2)	182 (46.8)	1.29 (0.99, 1.70)
2,4-D	28,871 (49.8)	262 (66.7)	1.06 (0.79, 1.43)
2,4,5-T	7264 (12.5)	116 (28.3)	1.57 (1.21, 2.04)
2,4,5-TP	3287 (5.5)	23 (5.5)	0.39 (0.25, 0.62)
Atrazine	25,297 (42.8)	237 (58.2)	1.03 (0.77, 1.38)
Cyanazine	14,641 (25.2)	133 (33.6)	0.90 (0.69, 1.18)
Metribuzin	15,500 (26.8)	137 (35.7)	0.86 (0.65, 1.14)

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; HR, Hazard Ratio; PD, Parkinson's disease.

[a] Exposed individuals who did not develop PD.

[b] Exposed individuals who developed PD.

[c] HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide).

[d] Hazard ratio allowed to vary by the median age (i.e., 63 years) for pesticides that did not meet proportional hazards assumption (p ≤ 0.10).

[e] Proportional hazards assumption did not meet for those in italics, but there was not adequate sample size meeting the criteria of at least five exposed cases in cross-classified categories.

without head injury [HR: 0.83 (95%CI: 0.61, 1.12), p for heterogeneity: 0.04]. The results were similar (i.e., no independent associations for the pesticide groups but heterogeneity by head injury for the mitochondrial complex I inhibitors), when we also considered participants as exposed if they indicated they used *at least one* individual pesticide in the group in the overall sample.

3.2. Pesticide exposure through Phase 2

Among male applicators, associations between ever-use of individual pesticides through Phase 2 were similar to the results using information reported at enrollment; specifically, PD risk was reduced among those who ever-used diazinon, ethylene dibromide, and 2,4,5-TP, and elevated among those who ever-used terbufos, 2,4,5-T, and trifluralin (Supplemental Table 7). Results that used IWLD through Phase 2 were also similar (Table 4).

4. Discussion

In this study, we found that ever-use of the insecticide terbufos and the herbicides trifluralin and 2,4,5-T was associated with elevated PD risk. Positive associations of PD with ever-use of the herbicides trifluralin and 2,4,5-T are consistent with the prior AHS-wide analysis based on 78 self-reported incident PD cases identified through Phase 2 (Kamel et al., 2007). We also found lower PD risk for ever-use of some pesticides including diazinon and 2,4,5-TP. In IWLD analyses, however, we did not

see evident monotonic exposure response gradients for these pesticides, although HRs for higher exposure categories reflected findings of ever-use analyses. We observed heterogeneity in the pesticide-PD associations by head injury and chemical-resistant gloves use, indicating higher PD risk for use of certain organochlorine insecticides (chlordane, DDT, and toxaphene), organophosphate insecticides (diazinon and phorate), insecticide permethrin, and herbicides (paraquat and pendimethalin) among those who reported head injury and for use of certain herbicides (dicamba, imazethapyr, and trifluralin) among those who did not use chemical-resistant gloves.

To the best of our knowledge, no studies have linked the insecticide terbufos with PD, although a few prior studies have linked other individual organophosphate insecticides that also act by inhibiting the enzyme acetylcholinesterase with PD (Gatto et al., 2009; Wang et al., 2014). We also found elevated PD risk in AHS applicators who were exposed to higher IWLD of the organophosphate insecticide dichlorvos. Chronic dichlorvos exposure in rats has been shown to induce degeneration of nigrostriatal dopaminergic neurons and alpha-synuclein aggregation, the hallmarks of PD pathogenesis, as well as to inhibit mitochondrial complexes and alter mitochondrial structures (Binukumar et al., 2010). We are aware of only one study on dichlorvos and PD, and in that study, individuals in the lower, although not the highest, exposure-day category of dichlorvos had elevated PD risk as compared to the individuals who were never exposed (van der Mark et al., 2014). On the other hand, we saw an inverse association between the organophosphate insecticide diazinon and PD risk in the overall sample and among those without head injury but saw elevated yet not statistically significant risk among those with head injury. A few prior studies, although not all, have linked diazinon with increased PD risk (Firestone et al., 2010; Gatto et al., 2009; Narayan et al., 2013). We observed

Table 3
Ever-use of pesticides reported at enrollment and Parkinson's disease (PD) risk by head injury status and chemical resistant glove use.

Pesticide	Head injury	Exposed/Unexposed PD cases	HR (95% CI)[a]	P[b]
Chlordane	No	77/206	1.10 (0.81, 1.51)	0.01
	Yes	16/6	4.08 (1.58, 10.55)	
Diazinon	No	57/223	0.64 (0.47, 0.88)	0.07
	Yes	10/11	1.48 (0.62, 3.51)	
DDT	No	87/189	0.86 (0.62, 1.19)	0.06
	Yes	15/7	2.12 (0.85, 5.31)	
Methyl bromide	No	22/265	0.67 (0.40, 1.11)	0.01
	Yes	6/15	2.85 (1.06, 7.65)	
Paraquat	No	45/239	1.00 (0.71, 1.41)	0.01
	Yes	10/12	3.20 (1.38, 7.45)	
Pendimethalin	No	65/207	0.90 (0.65, 1.25)	0.03
	Yes	10/6	2.85 (1.02, 7.91)	
Permethrin (animal and crop use combined)	No	33/260	0.79 (0.54, 1.14)	0.08
	Yes	6/12	2.04 (0.76, 5.44)	
Phorate	No	60/205	0.74 (0.53, 1.04)	0.03
	Yes	10/6	2.47 (0.89, 6.89)	
Toxaphene	No	31/248	0.69 (0.46, 1.03)	0.08
	Yes	7/15	1.64 (0.66, 4.04)	
	Chemical resistant glove[c]			
Dicamba	No	21/20	2.10 (1.11, 3.98)	0.008
	Yes	127/100	0.85 (0.63, 1.15)	
Imazethapyr	No	18/23	3.34 (1.75, 6.39)	0.0002
	Yes	100/127	0.92 (0.69, 1.24)	
Metalaxyl	No	8/39	0.44 (0.20, 0.96)	0.05
	Yes	48/191	1.00 (0.70, 1.43)	
Metolachlor	No	18/26	1.60 (0.88, 2.94)	0.01
	Yes	98/132	0.70 (0.54, 0.91)	
Metribuzin	No	17/25	1.48 (0.78, 2.81)	0.06
	Yes	110/109	0.78 (0.58, 1.06)	
Trifluralin	No	25/18	2.64 (1.42, 4.92)	0.03
	Yes	144/80	1.24 (0.91, 1.68)	

Abbreviation: CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; HR, Hazard Ratio; PD, Parkinson's disease.

[a] HR adjusted for state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide); HR for head injury also adjusted for sex.

[b] P-value for test for heterogeneity.

[c] Male applicators only.

similar heterogeneity by head injury for the organophosphate phorate. One prior study has reported an association between phorate exposure and elevated PD risk (Wang et al., 2014). Apart from a common pathway for pesticidal action, i.e., inhibition of acetylcholinesterase, individual organophosphate insecticides may exert neurotoxicity through a wide range of mechanisms including oxidative stress and neuroinflammation (Terry, 2012) resulting in varying degrees of toxicity. We are uncertain, however, about the reasons underlying the observed inverse association for some pesticides in the overall sample or among those without head injury.

Besides the prior AHS reports (Furlong et al., 2015; Kamel et al., 2007), we are not aware of other epidemiologic evidence linking the herbicides trifluralin and 2,4,5-T and PD, although an *in vitro* study has shown that trifluralin accelerates the formation of alpha-synuclein fibrils, a finding relevant to PD pathogenesis (Uversky et al., 2002). In another analysis, AHS applicators who experienced high pesticide exposure events involving trifluralin were also more likely to report olfactory impairment, one of the important prodromal symptoms of PD (Shrestha et al., 2019b). To our knowledge, the only other study (based on only four and seven exposed cases and controls respectively) that examined 2,4,5-T in relation to PD did not find any association (Dhillon et al., 2008). We found that the herbicide dicamba was associated with increased PD risk among those who did not use chemical-resistant gloves during handling of pesticides. Dicamba, structurally similar to the phenoxy herbicide 2,4,5-T (Bradberry et al., 2004), was associated with increased, although statistically non-significant, PD risk in the prior AHS investigation in the overall sample (Kamel et al., 2007). We observed an unexpected inverse association with the herbicide 2,4,5-TP, another phenoxy pesticide structurally similar to 2,4,5-T. Use of both 2,4,5-T and 2,4,5-TP was suspended in the US in 1979 due to potential contamination by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and associated health concerns (Gintautas et al., 1992; Lilienfeld and Gallo, 1989; Ware, 1988).

We found that ever-use of certain individual pesticides and the pesticide group mitochondrial complex I inhibitors was associated with increased PD risk among those who reported a history of head injury requiring medical attention, although head injury itself was not independently associated with elevated PD risk. While sequelae of traumatic brain injury, including microglial activation, alpha-synuclein aggregation, mitochondrial dysfunction, and other chronic inflammatory responses have been suggested as potential mechanisms for PD predisposition (Acosta et al., 2015; Hutson et al., 2011; Lifshitz et al., 2004; Loane et al., 2014), findings of prior epidemiologic studies on head injury and PD risk have been conflicting (Gardner et al., 2015; Kenborg et al., 2015; Taylor et al., 2016). With the notion that traumatic brain injury potentially requires synergistic factors to lead to PD, a case-control study examined PD risk in relation to joint exposure to head injury and paraquat (assessed using geographical information system-based land use and historic pesticide use reporting data); it found that paraquat-associated PD risk was greater among individuals with head injury and that the joint exposure was associated with higher PD risk as compared to exposure to paraquat or head injury alone (Lee et al., 2012). An experimental study in rats also demonstrated that acute traumatic brain injury induced progressive degeneration of nigrostriatal dopaminergic neurons, microglial activation, and alpha-synuclein accumulation were exacerbated when the animals were exposed to concentrations of paraquat that alone would not induce nigrostriatal death (Hutson et al., 2011). We are not aware of reports that examined interaction between other pesticides and head injury, but potential interaction is plausible as some of these pesticides have been implicated in PD pathogenesis (Furlong et al., 2015; Wang et al., 2014). We note several limitations in this particular analysis – our questionnaire did not capture head injury not requiring medical attention, and limited information was available on age at injury which precluded analysis on the timing of injury occurrence.

Although our subgroup analysis did hint at higher PD risk for paraquat as well as for the pesticide group mitochondrial complex I

inhibitors among individuals with head injury, we found limited evidence for independent associations of incident PD with these pesticides, whereas both were independently associated with PD in FAME (Tanner et al., 2011). Among other specific pesticides previously examined in FAME, we saw some suggestions of elevated PD risk for those with higher IWLD of the fungicide benomyl and the insecticide permethrin (animal use), though HR estimates were imprecise.

Limited reproducibility of FAME findings in the current study could be due to differences in study design, exposure data, and criteria for inclusion in analyses. FAME, although conducted within the AHS framework, collected more granular exposure data on some pesticides suspected to be etiologically relevant to PD, some of which were infrequently-used and therefore covered superficially at AHS enrollment (ever-use of "other pesticides"). The AHS questionnaires at enrollment focused, in part, on frequently-used pesticides. Further, AHS questionnaires differed for applicators and spouses, leading to lack of information in the AHS on certain pesticides of interest in FAME. For example, information on rotenone (included in the group mitochondrial complex I inhibitor) was not asked of spouses and was collected only from applicators who completed the take-home questionnaire. Likewise, although all participants were asked about ever-use of paraquat, information on duration and frequency of paraquat use was not asked of spouses and was collected only from the applicators returning the take-home questionnaire. Differences in study design and outcome ascertainment also could have contributed to differences in findings. Our analysis included all cohort members with at least some follow-up information and involved a longer follow-up period, whereas FAME involved a small subset of the cohort with fewer PD cases and shorter follow-up. Our current analysis utilized pesticide data obtained before PD diagnosis; whereas the exposure data in FAME were collected retrospectively after PD diagnosis (from participants or their proxies if participants were deceased), thereby opening the possibility of bias associated with differential recall of pesticide use (for example, if cases were more likely to recall such exposures). On the other hand, FAME benefitted from more detailed exposure information on relevant pesticides. Further, in FAME, both cases and controls underwent in-person assessment, while in the current study, we mainly relied on self-reports and those who self-reported to be PD-free did not undergo additional evaluation. Since we also included the FAME cases, however, a portion of our cases had an earlier in-person exam. Disease misclassification is possible and could have led to diminish estimates of relative risk in our analyses. In fact, while pesticide-use agreement was good overall, we did see some evidence of differential reporting by cases and controls in FAME when comparing data reported in both FAME and in the main AHS enrollment questionnaire (Supplemental Table 8 presents some comparisons, although we note that exposure timeframes are different as FAME asked exposures before PD diagnosis for cases or a reference date for controls). Lastly, FAME and our current cohort-wide effort are capturing different time windows of exposure relative to disease onset. The insidious onset of PD that is difficult to capture in non-clinical settings together with limited knowledge of induction and latent periods makes determination of exposure-relevant time windows difficult.

Specifically, for the herbicide paraquat, animal and earlier human studies offer persuasive evidence for a potential link with PD, despite continuing debate (Goldman et al., 2017; Jones et al., 2014). Some subgroups, including those with specific genetic makeup, head injury, and certain dietary intake have been found particularly vulnerable to PD following paraquat exposure (Goldman et al., 2012; Kamel et al., 2014; Lee et al., 2012; Ritz et al., 2009). We cannot rule out the possibility that limited evidence of independent associations between PD and ever-use of some pesticides (including paraquat) in the current study resulted from non-differential bias attenuating HR estimates; for example, the HR for ever-use of paraquat was elevated [HR: 1.09 (95% CI: 0.84, 1.41)], but not statistically significant. Nevertheless, we were still able to observe associations among those potentially more susceptible due to head injury.

Table 4
Intensity-weighted lifetime days of pesticide use at enrollment and incident PD in male applicators.

Pesticide	Lifetime days[a]	Pesticide exposure through enrollment				Lifetime days[a]	Pesticide exposure through Phase 2			
		No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]		No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]
Organochlorine insecticide										
Aldrin[d]	Never use	13,427 (82.7)	145 (75.5)	Ref	0.08	–	–	–	–	
	>0–≤315	994 (6.1)	18 (9.4)	0.84 (0.50, 1.42)						
	>315–≤980	911 (5.6)	17 (8.9)	0.82 (0.47, 1.41)						
	>980	905 (5.6)	12 (6.3)	0.56 (0.30, 1.06)						
Chlordane[d]	Never use	13,516 (80.7)	144 (72.7)	Ref	0.69	–	–	–	–	
	>0–≤236	1090 (6.5)	18 (9.1)	1.04 (0.63, 1.71)						
	>236–≤735	1111 (6.6)	17 (8.6)	0.92 (0.55, 1.53)						
	>735	1039 (6.2)	19 (9.6)	1.02 (0.62, 1.68)						
Dieldrin[d]	Never use	15,739 (96.2)	178 (93.2)	Ref	0.61	–	–	–	–	
	>0–≤338	307 (1.9)	8 (4.2)	1.24 (0.60, 2.59)						
	>338	308 (1.9)	5 (2.6)	0.77 (0.31, 1.93)						
DDT[d]	Never use	12,823 (78.3)	117 (60.6)	Ref	0.61	–	–	–	–	
	>0–≤341	1221 (7.5)	21 (10.9)	0.84 (0.52, 1.37)						
	>341–≤1675	1175 (7.2)	35 (18.1)	1.39 (0.92, 2.08)						
	>1675	1150 (7)	20 (10.4)	0.87 (0.53, 1.43)						
Heptachlor[d]	Never use	14,332 (87.4)	155 (78.7)	Ref	0.93	–	–	–	–	
	>0–≤280	673 (4.1)	14 (7.1)	1.41 (0.79, 2.51)						
	>280–≤882	729 (4.4)	17 (8.6)	1.44 (0.85, 2.46)						
	>882	660 (4)	11 (5.6)	1.02 (0.54, 1.94)						
Toxaphene[d]	Never use	16,128 (88.6)	200 (89.7)	Ref	0.12	–	–	–	–	
	>0–≤315	714 (3.9)	7 (3.1)	0.54 (0.26, 1.16)						
	>315–≤1181	670 (3.7)	8 (3.6)	0.66 (0.32, 1.33)						
	>1181	681 (3.7)	8 (3.6)	0.59 (0.29, 1.21)						
Lindane	Never use	15,591 (86.3)	186 (85.3)	Ref	0.56	Never use	15,424 (84.4)	183 (83.6)	Ref	0.62
	>0–≤315	823 (4.6)	7 (3.2)	0.56 (0.26, 1.2)		>0–≤341	944 (5.2)	8 (3.7)	0.59 (0.29, 1.21)	
	>315–≤1232	839 (4.6)	16 (7.3)	1.23 (0.73, 2.06)		>341–≤1232	961 (5.3)	18 (8.2)	1.26 (0.76, 2.07)	
	>1232	815 (4.5)	9 (4.1)	0.77 (0.40, 1.51)		>1232	940 (5.1)	10 (4.6)	0.80 (0.42, 1.51)	
Carbamate insecticide										
Carbaryl	Never use	9547 (57.8)	111 (56.3)	Ref	0.12	Never use	9194 (52)	106 (53)	Ref	0.11
	>0–≤387	2432 (14.7)	32 (16.2)	0.96 (0.65, 1.44)		>0–≤441	2904 (16.4)	37 (18.5)	0.90 (0.60, 1.36)	
	>387–≤2460	2403 (14.6)	30 (15.2)	0.81 (0.53, 1.26)		>441–≤2320	2918 (16.5)	30 (15)	0.78 (0.50, 1.22)	
	>2460	2123 (12.9)	24 (12.2)	0.64 (0.38, 1.08)		>2320	2675 (15.1)	27 (13.5)	0.63 (0.37, 1.05)	
Carbofuran[d]	-	–	–	–		Never use	23,500 (71.3)	198 (64.5)	Ref	0.41
						>0–≤368	3133 (9.5)	41 (13.4)	0.90 (0.60, 1.36)	
						>368–≤1370	3200 (9.7)	41 (13.4)	0.78 (0.50, 1.22)	
						>1370	3127 (9.5)	27 (8.8)	0.63 (0.37, 1.05)	
≤ 63y	Never use	13,827 (76.4)	52 (61.9)	Ref	0.28	...	...	...	...	
	>0–≤784	2156 (11.9)	24 (28.6)	1.88 (1.15, 3.05)						
	>784	2117 (11.7)	8 (9.5)	0.66 (0.31, 1.4)						
>63y	Never use	10,581 (67.5)	148 (66.4)	Ref	0.93					
	>0–≤784	2534 (16.2)	38 (17)	0.99 (0.69, 1.42)						
	>784	2551 (16.3)	37 (16.6)	1.02 (0.71, 1.46)						
Organophosphate insecticide										
Chlorpyrifos	Never use	18,564 (55)	191 (58.2)	Ref	0.60	Never use	19,755 (55.4)	220 (61.1)	Ref	0.78
	>0–≤455	5003 (14.8)	54 (16.5)	1.14 (0.84, 1.55)		>0–≤490	5251 (14.7)	55 (15.3)	1.04 (0.77, 1.41)	
	>455–≤1848	5165 (15.3)	33 (10.1)	0.68 (0.47, 0.99)		>490–≤1903	5406 (15.2)	38 (10.6)	0.71 (0.5, 1.01)	
	>1848	4994 (14.8)	50 (15.2)	1.12 (0.82, 1.54)		>1903	5243 (14.7)	47 (13.1)	0.99 (0.72, 1.35)	
Coumaphos	Never use	29,725 (91.2)	271 (90)	Ref	0.99	Never use	29,678 (91)	271 (90)	Ref	0.93
	>0–≤380	955 (2.9)	9 (3)	0.87 (0.45, 1.7)		>0–≤385	975 (3)	9 (3)	0.85 (0.44, 1.65)	
	>380–≤1418	979 (3)	12 (4)	1.07 (0.6, 1.91)		>385–≤1428	986 (3)	12 (4)	1.07 (0.6, 1.91)	
	>1418	938 (2.9)	9 (3)	0.99 (0.51, 1.92)		>1428	966 (3)	9 (3)	0.96 (0.49, 1.87)	
Diazinon[d]	*Never use*	*13,412 (79.2)*	*162 (81)*	*Ref*	*0.23*	Never use	13,202 (75.4)	162 (79.8)	Ref	0.11
	>0–≤328	*1194 (7.1)*	*13 (6.5)*	*0.79 (0.45, 1.40)*		>0–≤350	1443 (8.2)	13 (6.4)	0.68 (0.38, 1.21)	

Table 4 (*continued*)

Pesticide	Pesticide exposure through enrollment					Pesticide exposure through Phase 2				
	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]
	>328–≤1274	*1213 (7.2)*	*14 (7)*	*0.78 (0.45, 1.35)*		*>350–≤1270*	1476 (8.4)	16 (7.9)	0.81 (0.48, 1.36)	
	>1274	*1116 (6.6)*	*11 (5.5)*	*0.69 (0.37, 1.29)*		*>1270*	1391 (7.9)	12 (5.9)	0.6 (0.32, 1.12)	
Dichlorvos	Never use	29,516 (89.2)	264 (86.3)	Ref	0.06	Never use	29,409 (88.9)	264 (86.3)	Ref	0.06
	>0–≤1344	1783 (5.4)	15 (4.9)	0.79 (0.46, 1.33)		>0–≤1360	1844 (5.6)	15 (4.9)	0.79 (0.46, 1.33)	
	>1344	1773 (5.4)	27 (8.8)	1.46 (0.98, 2.19)		>1360	1832 (5.5)	27 (8.8)	1.46 (0.98, 2.19)	
Fonofos	Never use	25,838 (77.6)	240 (77.4)	Ref	0.32	Never use	25,820 (77.5)	240 (77.4)	Ref	0.32
	>0–≤455	2467 (7.4)	26 (8.4)	1.06 (0.7, 1.61)		>0–≤455	2468 (7.4)	26 (8.4)	1.06 (0.7, 1.61)	
	>455–≤1680	2526 (7.6)	24 (7.7)	0.92 (0.60, 1.42)		>455–≤1696	2538 (7.6)	24 (7.7)	0.92 (0.6, 1.42)	
	>1680	2463 (7.4)	20 (6.5)	0.80 (0.50, 1.27)		>1696	2470 (7.4)	20 (6.5)	0.8 (0.5, 1.27)	
Malathion	Never use	6436 (35.7)	76 (35)	Ref	0.08	Never use	6107 (30.4)	69 (29.2)	Ref	0.12
	>0–≤368	3832 (21.3)	53 (24.4)	1.13 (0.79, 1.61)		>0–≤384	4797 (23.9)	68 (28.8)	1.26 (0.89, 1.79)	
	>368 ≤ 1440	3948 (21.9)	46 (21.2)	0.89 (0.62, 1.29)		>384–≤1344	4603 (22.9)	47 (19.9)	0.93 (0.64, 1.35)	
	>1440	3795 (21.1)	42 (19.4)	0.75 (0.51, 1.10)		>1344	4584 (22.8)	52 (22)	0.83 (0.57, 1.2)	
Parathion	Never use	16,605 (92.1)	201 (91)	Ref	0.97	Never use	16,580 (91.9)	201 (90.5)	Ref	0.76
	>0–≤882	718 (4)	10 (4.5)	0.94 (0.49, 1.78)		>0–≤880	728 (4)	10 (4.5)	0.86 (0.44, 1.69)	
	>882	697 (3.9)	10 (4.5)	0.99 (0.52, 1.89)		>880	726 (4)	11 (5)	1.05 (0.56, 1.94)	
Phorate	Never use	11,467 (68.4)	121 (61.4)	Ref	0.55	Never use	11,523 (67.8)	122 (61.3)	Ref	0.47
	>0–≤315	1771 (10.6)	25 (12.7)	1.18 (0.75, 1.86)		>0–≤320	1818 (10.7)	25 (12.6)	1.14 (0.72, 1.79)	
	>315–≤1176	1809 (10.8)	34 (17.3)	1.61 (1.07, 2.41)		>320–≤1176	1874 (11)	35 (17.6)	1.62 (1.09, 2.41)	
	>1176	1715 (10.2)	17 (8.6)	0.84 (0.50, 1.40)		>1176	1781 (10.5)	17 (8.5)	0.8 (0.48, 1.34)	
Terbufos	Never use	19,869 (59.8)	168 (54.4)	Ref	0.50	Never use	19,649 (59.1)	168 (54)	Ref	0.53
	>0–≤646	4397 (13.2)	46 (14.9)	1.34 (0.96, 1.88)		>0–≤660	4497 (13.5)	48 (15.4)	1.35 (0.97, 1.89)	
	>646–≤2400	4536 (13.7)	54 (17.5)	1.46 (1.06, 2.00)		>660–≤2436	4623 (13.9)	53 (17)	1.39 (1.01, 1.91)	
	>2400	4411 (13.3)	41 (13.3)	1.16 (0.82, 1.65)		>2436	4480 (13.5)	42 (13.5)	1.16 (0.82, 1.64)	
Permethrin insecticide										
Permethrin (crops)	Never use	28,383 (86.5)	269 (89.4)	Ref	0.21	Never use	27,839 (84.8)	265 (88.3)	Ref	0.27
	>0–≤273	1470 (4.5)	15 (5)	1.30 (0.77, 2.2)		>0–≤288	1639 (5)	17 (5.7)	1.19 (0.7, 2.01)	
	>273–≤1080	1492 (4.5)	11 (3.7)	1.01 (0.55, 1.84)		>288–≤1117	1695 (5.2)	11 (3.7)	0.94 (0.51, 1.72)	
	>1080	1466 (4.5)	6 (2)	0.59 (0.26, 1.33)		>1117	1643 (5)	7 (2.3)	0.66 (0.31, 1.4)	
Permethrin (animals)	Never use	28,783 (86.3)	272 (88.6)	Ref	0.21	Never use	28,163 (84.3)	270 (87.9)	Ref	0.16
	>0–≤368	1574 (4.7)	11 (3.6)	0.93 (0.50, 1.70)		>0–≤392	1737 (5.2)	11 (3.6)	0.84 (0.46, 1.53)	
	>368–≤1418	1505 (4.5)	9 (2.9)	0.77 (0.40, 1.51)		>392–≤1512	1781 (5.3)	9 (2.9)	0.68 (0.34, 1.35)	
	>1418	1493 (4.5)	15 (4.9)	1.44 (0.85, 2.44)		>1512	1721 (5.2)	17 (5.5)	1.49 (0.9, 2.46)	
Fumigant										
Carbon disulfide/carbon tetrachloride [d]	Never use	17,467 (95.8)	209 (94.6)	Ref	0.74	--	--	--	--	
	>0–≤172	398 (2.2)	6 (2.7)	0.82 (0.36, 1.86)						
	>172	364 (2)	6 (2.7)	0.88 (0.39, 1.98)						
Methyl Bromide	Never use	28,072 (84.9)	274 (85.9)	Ref	0.58	Never use	28,084 (84.8)	276 (85.7)	Ref	0.52
	>0–≤320	1613 (4.9)	13 (4.1)	0.82 (0.46, 1.47)		>0–≤326	1669 (5)	14 (4.3)	0.78 (0.44, 1.41)	
	>320–≤1372	1670 (5.1)	17 (5.3)	1.03 (0.60, 1.78)		>326–≤1395	1673 (5.1)	17 (5.3)	0.98 (0.57, 1.7)	
	>1372	1706 (5.2)	15 (4.7)	0.82 (0.46, 1.48)		>1395	1696 (5.1)	15 (4.7)	0.8 (0.45, 1.42)	
Fungicide										
Benomyl	Never use	14,990 (92.8)	174 (91.6)	Ref	0.31	Never use	14,977 (92.4)	174 (90.6)	Ref	0.35
	>0–≤868	591 (3.7)	5 (2.6)	0.62 (0.24, 1.61)		>0–≤868	623 (3.8)	6 (3.1)	0.73 (0.31, 1.75)	
	>868	574 (3.6)	11 (5.8)	1.34 (0.64, 2.80)		>868	613 (3.8)	12 (6.3)	1.34 (0.64, 2.79)	
Captan	Never use	29,167 (89.8)	274 (90.7)	Ref	0.36	Never use	28,708 (88.2)	270 (88.8)	Ref	0.26
	>0–≤9	1224 (3.8)	8 (2.6)	0.83 (0.41, 1.68)		>0–≤10	1278 (3.9)	8 (2.6)	0.78 (0.39, 1.59)	
	>9–≤212	1046 (3.2)	6 (2)	0.65 (0.29, 1.46)		>10–≤540	1311 (4)	10 (3.3)	0.83 (0.44, 1.57)	
	>212	1060 (3.3)	14 (4.6)	1.27 (0.74, 2.20)		>540	1264 (3.9)	16 (5.3)	1.33 (0.80, 2.21)	
Chlorothalonil	Never use	30,547 (92.8)	293 (94.2)	Ref	0.41	Never use	30,371 (92.2)	291 (93.6)	Ref	0.47
	>0–≤1535	1132 (3.4)	7 (2.3)	0.74 (0.34, 1.61)		>0–≤1613	1245 (3.8)	7 (2.3)	0.71 (0.32, 1.55)	
	>1535	1221 (3.7)	11 (3.5)	1.29 (0.66, 2.56)		>1613	1312 (4)	13 (4.2)	1.41 (0.75, 2.66)	
Maneb[e]	-	–	–	–		Never use	15,464 (92.3)	186 (93)	Ref	0.34
						>0–≤1268	660 (3.9)	8 (4)	0.69 (0.31, 1.53)	
						>1268	636 (3.8)	6 (3)	0.59 (0.25, 1.4)	

Table 4 (*continued*)

		Pesticide exposure through enrollment				Pesticide exposure through Phase 2				
Pesticide	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]
Metalaxyl	Never use	14,301 (81.6)	177 (82.3)	Ref	0.14	Never use	14,239 (79.1)	175 (80.6)	Ref	0.47
	>0–≤312	1060 (6.1)	17 (7.9)	1.27 (0.77, 2.11)		>0–≤312	1241 (6.9)	18 (8.3)	1.26 (0.76, 2.08)	
	>312–≤1568	1094 (6.2)	15 (7)	1.18 (0.66, 2.11)		>312–≤1488	1286 (7.1)	15 (6.9)	1.17 (0.64, 2.13)	
	>1568	1061 (6.1)	6 (2.8)	0.53 (0.22, 1.27)		>1488	1240 (6.9)	9 (4.1)	0.79 (0.38, 1.65)	
Herbicide										
Alachlor	Never use	15,100 (45.7)	127 (41.9)	Ref	0.80	Never use	14,974 (45.3)	124 (40.9)	Ref	0.73
	>0–≤809	5925 (18)	63 (20.8)	1.11 (0.82, 1.52)		>0–≤809	6011 (18.2)	65 (21.5)	1.15 (0.85, 1.57)	
	>809–≤3132	6056 (18.3)	55 (18.2)	0.95 (0.69, 1.30)		>809–≤3145	6121 (18.5)	56 (18.5)	0.97 (0.7, 1.33)	
	>3132	5927 (18)	58 (19.1)	1.07 (0.78, 1.46)		>3145	5977 (18.1)	58 (19.1)	1.09 (0.8, 1.5)	
Butylate	Never use	11,964 (71.9)	144 (72.7)	Ref	0.22	Never use	13,263 (73)	164 (73.9)	Ref	0.24
	>0–≤473	1564 (9.4)	25 (12.6)	1.26 (0.81, 1.95)		>0–≤473	1626 (9)	26 (11.7)	1.26 (0.81, 1.95)	
	>473–≤1519	1583 (9.5)	16 (8.1)	0.85 (0.50, 1.45)		>473–≤1512	1659 (9.1)	18 (8.1)	0.91 (0.54, 1.53)	
	>1519	1531 (9.2)	13 (6.6)	0.73 (0.41, 1.30)		>1512	1619 (8.9)	14 (6.3)	0.73 (0.41, 1.3)	
Chlorimuron Ethyl	Never use	12,384 (68)	163 (73.4)	Ref	0.44	Never use	12,187 (65.4)	162 (72.6)	Ref	0.22
	>0–≤245	1930 (10.6)	25 (11.3)	1.22 (0.80, 1.87)		>0–≤263	2140 (11.5)	30 (13.5)	1.28 (0.85, 1.9)	
	>245–≤784	1977 (10.9)	17 (7.7)	0.80 (0.49, 1.33)		>263–≤817	2169 (11.6)	15 (6.7)	0.69 (0.4, 1.18)	
	>784	1910 (10.5)	17 (7.7)	0.85 (0.52, 1.41)		>817	2127 (11.4)	16 (7.2)	0.77 (0.46, 1.28)	
Dicamba	Never use	15,344 (47.7)	141 (48)	Ref	0.33	Never use	14,269 (44.3)	131 (44.4)	Ref	0.13
	>0–≤564	5548 (17.2)	50 (17)	0.90 (0.63, 1.28)		>0–≤694	5897 (18.3)	58 (19.7)	0.99 (0.7, 1.41)	
	>564–≤2184	5761 (17.9)	46 (15.6)	0.81 (0.56, 1.17)		>694–≤2380	6126 (19)	43 (14.6)	0.83 (0.56, 1.22)	
	>2184	5524 (17.2)	57 (19.4)	1.11 (0.79, 1.56)		>2380	5950 (18.5)	63 (21.4)	1.25 (0.88, 1.77)	
EPTC	Never use	26,190 (79.7)	249 (83)	Ref	0.74	Never use	26,155 (79.6)	249 (83)	Ref	0.73
	>0–≤315	2215 (6.7)	19 (6.3)	0.93 (0.58, 1.49)		>0–≤315	2222 (6.8)	19 (6.3)	0.93 (0.58, 1.49)	
	>315–≤1181	2245 (6.8)	14 (4.7)	0.67 (0.39, 1.15)		>315–≤1190	2261 (6.9)	14 (4.7)	0.66 (0.39, 1.14)	
	>1181	2192 (6.7)	18 (6)	0.97 (0.60, 1.57)		>1190	2205 (6.7)	18 (6)	0.97 (0.6, 1.57)	
Glyphosate	Never use	8307 (23.3)	86 (24.2)	Ref	0.09	Never use	5247 (14.8)	62 (17.5)	Ref	0.10
	>0–≤677	8996 (25.2)	106 (29.8)	1.17 (0.88, 1.55)		>0–≤970	9965 (28)	132 (37.2)	1.21 (0.88, 1.65)	
	>677–<2604	9313 (26.1)	91 (25.6)	0.99 (0.73, 1.33)		>970–≤3352	10,318 (29)	84 (23.7)	0.92 (0.64, 1.34)	
	>2604	9015 (25.3)	73 (20.5)	0.85 (0.62, 1.17)		>3352	10,018 (28.2)	77 (21.7)	0.88 (0.62, 1.25)	
Imazethapyr	Never use	17,941 (55.5)	173 (58.6)	Ref	0.38	Never use	17,152 (53.1)	169 (56.9)	Ref	0.64
	>0–≤341	4874 (15.1)	42 (14.2)	1.00 (0.70, 1.45)		>0–≤403	5007 (15.5)	47 (15.8)	1.03 (0.72, 1.47)	
	>341–≤1008	4752 (14.7)	41 (13.9)	1.05 (0.73, 1.52)		>403–≤1176	5205 (16.1)	42 (14.1)	0.92 (0.63, 1.35)	
	>1008	4733 (14.7)	39 (13.2)	1.18 (0.81, 1.72)		>1176	4964 (15.4)	39 (13.1)	1.11 (0.76, 1.62)	
Metolachlor	Never use	17,519 (52.8)	182 (60.1)	Ref	0.79	Never use	16,273 (49)	174 (57.4)	Ref	0.71
	>0–≤720	5255 (15.8)	35 (11.6)	0.67 (0.46, 0.96)		>0–≤760	5600 (16.9)	41 (13.5)	0.72 (0.51, 1.03)	
	>720–≤2688	5322 (16)	44 (14.5)	0.84 (0.6, 1.17)		>760–≤2700	5776 (17.4)	44 (14.5)	0.78 (0.55, 1.1)	
	>2688	5079 (15.3)	42 (13.9)	0.90 (0.64, 1.26)		>2700	5585 (16.8)	44 (14.5)	0.89 (0.63, 1.25)	
Paraquat	Never use	15,305 (84.1)	188 (82.5)	Ref	0.45	Never use	15,216 (81.9)	188 (81.7)	Ref	0.36
	>0–≤289	961 (5.3)	13 (5.7)	1.03 (0.58, 1.81)		>0–≤308	1111 (6)	13 (5.7)	0.92 (0.51, 1.63)	
	>289–≤1232	975 (5.4)	18 (7.9)	1.42 (0.86, 2.33)		>308–≤1308	1135 (6.1)	20 (8.7)	1.49 (0.92, 2.41)	
	>1232	960 (5.3)	9 (3.9)	0.74 (0.37, 1.49)		>1308	1113 (6)	9 (3.9)	0.69 (0.34, 1.38)	
Pendimethalin	Never use	11,440 (62.9)	154 (68.1)	Ref	0.25	Never use	10,685 (53.9)	145 (60.9)	Ref	0.57
	>0–≤341	2262 (12.4)	32 (14.2)	1.13 (0.77, 1.66)		>0–≤378	3003 (15.2)	38 (16)	1.1 (0.77, 1.57)	
	>341–≤1320	2263 (12.4)	23 (10.2)	0.90 (0.58, 1.40)		>378 ≤ 1232	3114 (15.7)	32 (13.4)	0.97 (0.65, 1.44)	
	>1320	2227 (12.2)	17 (7.5)	0.76 (0.46, 1.26)		>1232	3005 (15.2)	23 (9.7)	0.89 (0.57, 1.39)	
Petroleum	Never use	14,257 (78.9)	184 (83.6)	Ref	0.72	Never use	14,169 (78.1)	183 (82.8)	Ref	0.59
	>0–≤515	1266 (7)	9 (4.1)	0.57 (0.29, 1.11)		>0–≤495	1317 (7.3)	11 (5)	0.67 (0.36, 1.23)	
	>515–≤2500	1286 (7.1)	13 (5.9)	0.91 (0.52, 1.61)		>495–≤2408	1355 (7.5)	13 (5.9)	0.88 (0.5, 1.55)	
	>2500	1261 (7)	14 (6.4)	0.89 (0.52, 1.53)		>2408	1312 (7.2)	14 (6.3)	0.85 (0.49, 1.47)	
Trifluralin	Never use	14,464 (45.7)	116 (40.4)	Ref	0.07	Never use	14,106 (44.5)	113 (39.4)	Ref	0.10
	>0–≤1008	5653 (17.9)	61 (21.3)	1.40 (1.01, 1.95)		>0–≤1046	5779 (18.2)	64 (22.3)	1.42 (1.02, 1.97)	
	>1008–≤3828	5877 (18.6)	47 (16.4)	1.05 (0.73, 1.52)		>1046–≤3906	6144 (19.4)	49 (17.1)	1.05 (0.73, 1.52)	
	>3828	5669 (17.9)	63 (22)	1.50 (1.06, 2.11)		>3906	5672 (17.9)	61 (21.3)	1.48 (1.04, 2.1)	
2,4-D	Never use	8108 (22.9)	72 (20.5)	Ref	0.52	Never use	6928 (19.5)	67 (18.9)	Ref	0.52

Table 4 (*continued*)

Pesticide	Lifetime days[a]	Pesticide exposure through enrollment				Pesticide exposure through Phase 2				
		No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]
	>0–≤1269	8944 (25.3)	84 (23.9)	1.07 (0.78, 1.47)		>0–≤1440	9486 (26.6)	97 (27.3)	1.08 (0.79, 1.49)	
	>1269–≤5104	9303 (26.3)	97 (27.6)	1.04 (0.76, 1.43)		>1440–≤5394	9767 (27.4)	86 (24.2)	0.87 (0.62, 1.22)	
	>5104	9035 (25.5)	99 (28.1)	0.96 (0.7, 1.31)		>5394	9432 (26.5)	105 (29.6)	0.93 (0.67, 1.29)	
2,4,5-T [d]	Never use	13,328 (80.9)	143 (71.9)	Ref	0.71	--	--	--	--	
	>0–≤289	1068 (6.5)	20 (10.1)	1.21 (0.75, 1.95)						
	>289–≤1006	1069 (6.5)	20 (10.1)	1.27 (0.78, 2.05)						
	>1006	1007 (6.1)	16 (8)	1.11 (0.65, 1.89)						
Atrazine	Never use	9709 (27.3)	95 (27)	Ref	0.64	Never use	8473 (23.8)	87 (24.7)	Ref	0.53
	>0–≤1050	8525 (23.9)	87 (24.7)	1.14 (0.84, 1.54)		>0–≤1221	8960 (25.2)	97 (27.6)	1.17 (0.86, 1.59)	
	>1050–≤4456	8826 (24.8)	85 (24.1)	0.99 (0.73, 1.34)		>1221–≤4666	9250 (26)	83 (23.6)	0.95 (0.69, 1.3)	
	>4456	8556 (24)	85 (24.1)	0.99 (0.73, 1.34)		>4666	8943 (25.1)	85 (24.1)	0.98 (0.72, 1.34)	
Cyanazine	Never use	19,018 (57.2)	174 (57.4)	Ref	0.79	Never use	18,910 (56.9)	173 (57.1)	Ref	0.66
	>0–≤560	4706 (14.2)	40 (13.2)	0.84 (0.59, 1.20)		>0–≤588	4808 (14.5)	39 (12.9)	0.81 (0.57, 1.17)	
	>560–≤2268	4850 (14.6)	45 (14.9)	0.91 (0.64, 1.28)		>588–≤2279	4792 (14.4)	46 (15.2)	0.94 (0.66, 1.32)	
	>2268	4665 (14)	44 (14.5)	1.00 (0.71, 1.42)		>2279	4716 (14.2)	45 (14.9)	1.03 (0.73, 1.45)	
Metribuzin	Never use	9599 (59.7)	115 (61.5)	Ref	0.33	Never use	9513 (58)	115 (60.8)	Ref	0.37
	>0–≤319	2148 (13.4)	30 (16)	1.10 (0.71, 1.69)		>0–≤341	2358 (14.4)	31 (16.4)	1.01 (0.65, 1.56)	
	>319–≤1024	2193 (13.6)	21 (11.2)	0.77 (0.47, 1.27)		>341–≤1054	2259 (13.8)	21 (11.1)	0.75 (0.46, 1.23)	
	>1024	2128 (13.2)	21 (11.2)	0.81 (0.49, 1.33)		>1054	2260 (13.8)	22 (11.6)	0.81 (0.50, 1.34)	

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; HR, Hazard Ratio.

[a] Tertile cut-off and n (%) may differ between Phase 1 and Phase 2 exposure because of difference in exposure information and missingness.

[b] HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation $\geq$ 0.40 with the ever-use variable of the target pesticide).

[c] P-value for test for trend.

[d] HR not presented if, at Phase 2, pesticide exposure since enrollment was not reported.

[e] HR allowed to vary by the median age (i.e., 63 years) for pesticides that did not meet proportional hazards assumption (p $\leq$ 0.10).

[f] Proportional hazards assumption not met for those in italics, but there was no adequate sample size to provide stratified estimates by the median age.

[g] HR not presented as there were less than 5 exposed cases.

Our study also suggests that use of chemical resistant gloves may have conferred some protection against PD in pesticide applicators using certain herbicides. Chemical resistant gloves, but not other types of gloves, have been shown in the AHS to offer protection from pesticide exposure (Hines et al., 2011; Thomas et al., 2010). In FAME, associations of several pesticides including permethrin and paraquat with PD risks were greater in those who used chemical-resistant gloves less than 50% of the time compared to those who used >50% (Furlong et al., 2015).

4.1. Limitations and strengths

Our study has several limitations. First, pesticide-use data were self-reported; thus, some exposure misclassification is likely. However, AHS farmers have been shown to report both reliable and valid pesticide usage (Blair et al., 2002; Hoppin et al., 2002); for lifetime exposures, we used exposure intensity, which correlates better with urinary biomarkers of pesticides than uncorrected days of use (Coble et al., 2011; Hines et al., 2011). Due to our prospective design, exposure misclassification was likely non-differential for PD. Non-differential misclassification might have biased effect estimates towards the null for binary pesticide-use variables; but, for polytomous categories, directionality of bias is uncertain (Rothman et al., 2008).

Second, in the current analyses, although we incorporated pesticide usage through the first follow-up for applicators, we could not do so for spouses and we could not account for more proximal exposures for applicators because data were not available for all participants due to cohort attrition. The time duration from Phase 2 (when exposures were updated for this analysis) to Phase 4 (i.e., end of follow-up) was 13 years on average. Failure to account for exposure occurring during this window could have heightened exposure misclassification, for those pesticides that are still on the market.

Third, our effort to validate all potential PD cases using medical records suffered from low response from both participants (or their proxies) and their physicians, so we relied on PD self-report. We attempted to minimize potential PD misclassification by restricting analysis to individuals providing consistent responses on PD across surveys and for those with relevant questionnaire data, restricting to cases with supporting data on neurological symptoms and medication use. We did find that those medical records we obtained were in high agreement with self-reported PD. Further, agreement between PD self-report and clinical diagnostic evaluation was found to be high in FAME (84%) (Tanner et al., 2011) as well in other studies (Jain et al., 2015), indicating PD self-reports are, in general, reasonably reliable. Furthermore, we observed reduced PD risk in smokers [age and sex adjusted HR: 0.75 (95%CI: 0.61, 0.91) for former smoking and 0.55 (95%CI: 0.38, 0.81) for current smoking] in the current study, which is consistent with prior literature (Hernan et al., 2002) and thus indirectly supports the validity of PD self-reports in the AHS.

Fourth, we were unable to account for possible PD in participants who were lost to follow-up, although we were able to identify participants who had PD recorded on their death certificates (but did not report PD in surveys). We included such cases in our analysis if their proxy provided adequate information in the validation screener to support a PD diagnosis. We had similar results in analyses using inverse probability weighting to make inference on all enrolled participants. Nevertheless, we cannot completely rule out selection bias due to loss-to-follow up or bias due to selective mortality before enrollment resulting from higher pesticide exposures. Fifth, we found inverse associations for some pesticides which may be due to reverse causality – for instance, if individuals with symptomatic but undiagnosed PD accumulate less exposure due to reduced farming activities compared to those individuals that are "healthy" and continue farming. We know of no reason why this reverse causality would apply only to certain pesticides.

Sixth, we also did not adjust for multiple comparisons given the exploratory nature of our study and therefore some of the observed associations may be false positives and thus our findings should be interpreted with caution. Seventh, participants were exposed to multiple pesticides. Although we adjusted for several correlated pesticides, we cannot rule out lack of complete control of confounding due to other pesticides. Lastly, our current analytical approach focusing on a single exposure fails to account for the overall PD risk associated with multiple pesticide exposures. Pesticide use in the AHS is not easily addressed using current methods for the analysis of chemical mixtures. Applicators report a lifetime of use, with one or two possibly different pesticides being used in any given year. Chemicals used may have changed over time in relation to specific crops planted, environmental conditions, changes in availability of banned or restricted chemicals, pesticide costs and economic constraints, and much more. The development and application of new methods to address this complex and unique mixture situation is warranted.

Countering these limitations, the strengths for the current investigation include large sample size, prospective design, long-term follow-up, comprehensive information on lifetime use of pesticides, and detailed information on PD risk factors. Although we found evidence of increased PD risk for a few pesticides, most pesticides were not associated with PD nor, for the most part, were pesticides/groups that were previously implicated for PD. Continued research on pesticide-PD risk that can focus on specific chemicals is important because of continued widespread use of pesticides worldwide.

Credit author statement

Srishti Shrestha and Dale P. Sandler conceptualized the investigation, led the analysis and prepared the first draft of the manuscript. Srishti Shrestha and Marie Richards-Barber conducted data analysis. Dale P. Sandler provided supervision and funding acquisition. Dale P. Sandler, Christine G. Parks, and Laura E. Beane Freeman were involved in project administration. All the authors were involved in data interpretation and in reviewing, critiquing, and editing the manuscript, and provided final manuscript approval.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

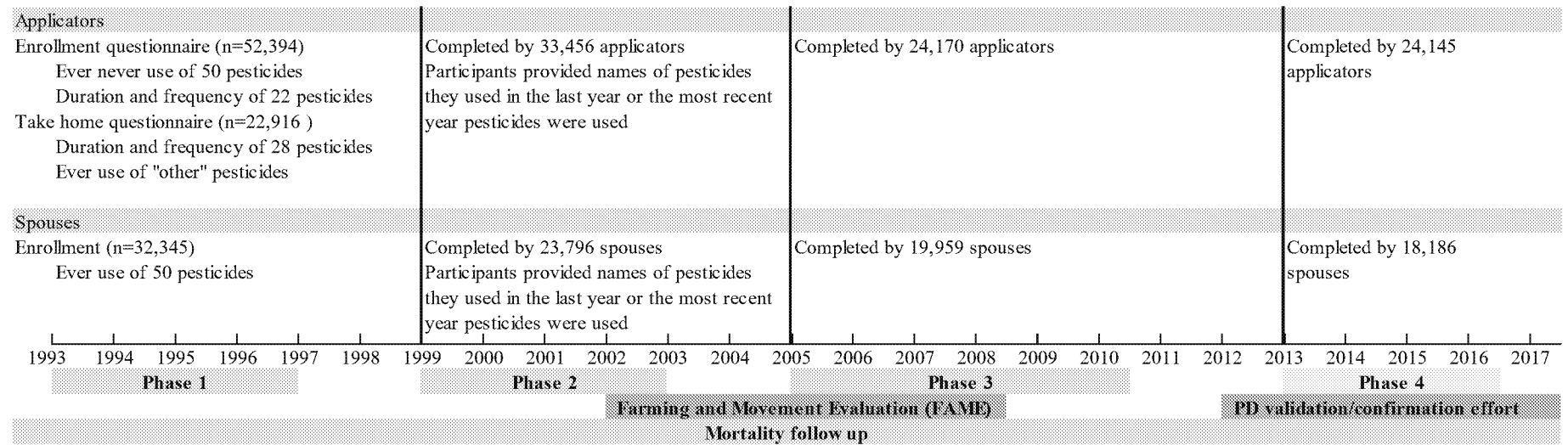Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.110186.

References

Acosta, S.A., Tajiri, N., de la Pena, I., Bastawrous, M., Sanberg, P.R., Kaneko, Y., Borlongan, C.V., 2015. Alpha-synuclein as a pathological link between chronic
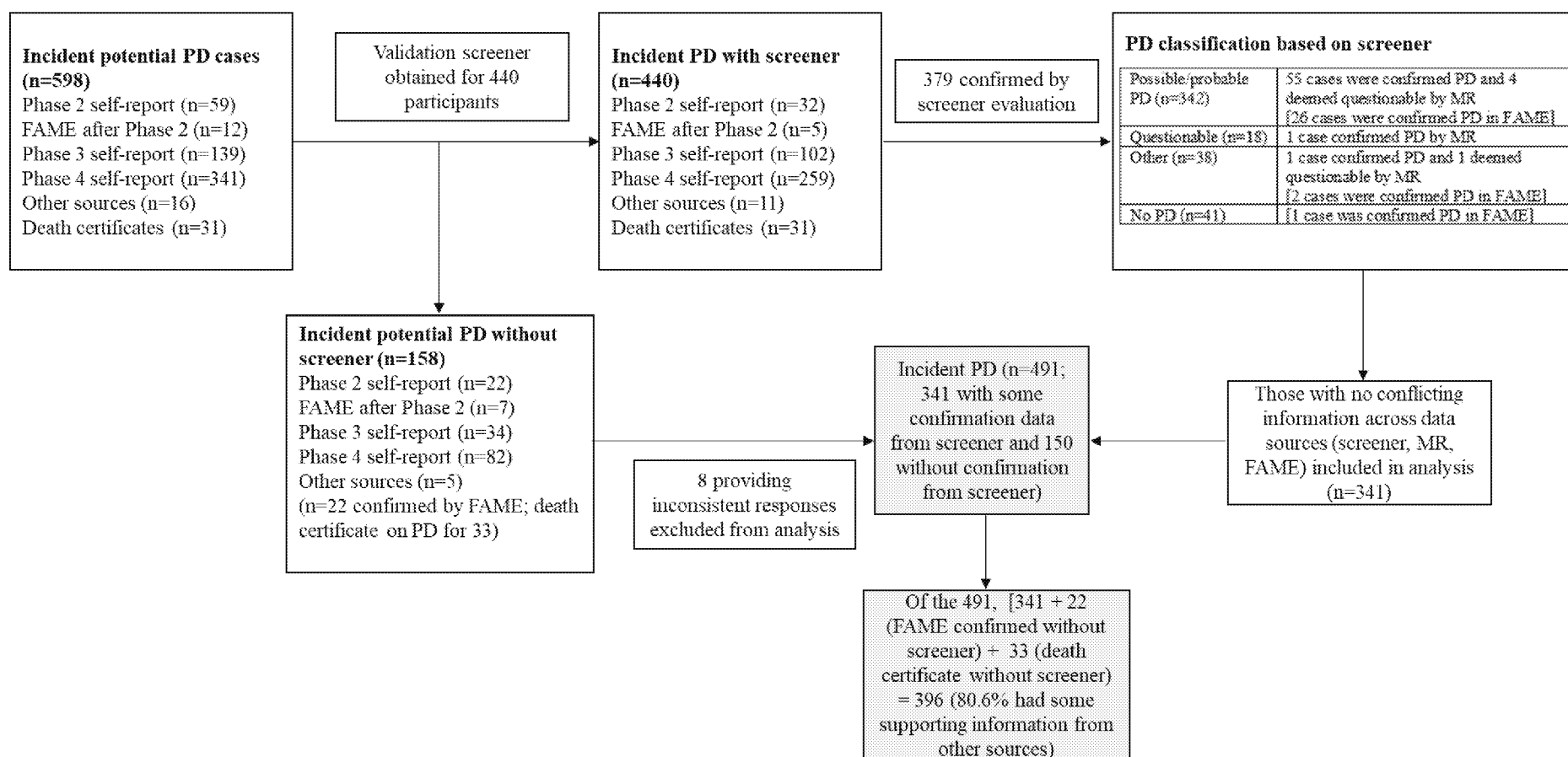
traumatic brain injury and Parkinson's disease. J. Cell. Physiol. 230, 1024–1032. https://doi.org/10.1002/jcp.24830.

Alavanja, M.C., Sandler, D.P., McMaster, S.B., Zahm, S.H., McDonnell, C.J., Lynch, C.F., Pennybacker, M., Rothman, N., Dosemeci, M., Bond, A.E., Blair, A., 1996. The agricultural health study. Environ. Health Perspect. 104, 362–369. https://doi.org/10.1289/ehp.96104362.

Atwood, D., Paisley-Jones, C., 2017. Pesticides Industry Sales and Usage 2008-2012 Market Estimates. United States Environmental Protection Agency, Washington, D.C.

Binukumar, B.K., Bal, A., Kandimalla, R.J., Gill, K.D., 2010. Nigrostriatal neuronal death following chronic dichlorvos exposure: crosstalk between mitochondrial impairments, alpha synuclein aggregation, oxidative damage and behavioral changes. Mol. Brain 3, 35. https://doi.org/10.1186/1756-6606-3-35.

Blair, A., Tarone, R., Sandler, D., Lynch, C.F., Rowland, A., Wintersteen, W., Steen, W.C., Samanic, C., Dosemeci, M., Alavanja, M.C., 2002. Reliability of reporting on lifestyle and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 13, 94–99. https://doi.org/10.1097/00001648-200201000-00015.

Bradberry, S.M., Proudfoot, A.T., Vale, J.A., 2004. Poisoning due to chlorophenoxy herbicides. Toxicol. Rev. 23, 65–73. https://doi.org/10.2165/00139709-200423020-00001.

Coble, J., Thomas, K.W., Hines, C.J., Hoppin, J.A., Dosemeci, M., Curwin, B., Lubin, J.H., Beane Freeman, L.E., Blair, A., Sandler, D.P., Alavanja, M.C., 2011. An updated algorithm for estimation of pesticide exposure intensity in the Agricultural Health Study. Int. J. Environ. Res. Publ. Health 8, 4608–4622. https://doi.org/10.3390/ijerph8124608.

Dhillon, A.S., Tarbutton, G.L., Levin, J.L., Plotkin, G.M., Lowry, L.K., Nalbone, J.T., Shepherd, S., 2008. Pesticide/environmental exposures and Parkinson's disease in East Texas. J. Agromed. 13, 37–48. https://doi.org/10.1080/10599240801986215.

Firestone, J.A., Lundin, J.I., Powers, K.M., Smith-Weller, T., Franklin, G.M., Swanson, P. D., Longstreth Jr., W.T., Checkoway, H., 2010. Occupational factors and risk of Parkinson's disease: a population-based case-control study. Am. J. Ind. Med. 53, 217–223. https://doi.org/10.1002/ajim.20788.

Fitzmaurice, A.G., Rhodes, S.L., Lulla, A., Murphy, N.P., Lam, H.A., O'Donnell, K.C., Barnhill, L., Casida, J.E., Cockburn, M., Sagasti, A., Stahl, M.C., Maidment, N.T., Ritz, B., Bronstein, J.M., 2013. Aldehyde dehydrogenase inhibition as a pathogenic mechanism in Parkinson disease. Proc. Natl. Acad. Sci. U. S. A. 110, 636–641. https://doi.org/10.1073/pnas.1220399110.

Fitzmaurice, A.G., Rhodes, S.L., Cockburn, M., Ritz, B., Bronstein, J.M., 2014. Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease. Neurology 82, 419–426. https://doi.org/10.1212/WNL.0000000000000083.

Furlong, M., Tanner, C.M., Goldman, S.M., Bhudhikanok, G.S., Blair, A., Chade, A., Comyns, K., Hoppin, J.A., Kasten, M., Korell, M., Langston, J.W., Marras, C., Meng, C., Richards, M., Ross, G.W., Umbach, D.M., Sandler, D.P., Kamel, F., 2015. Protective glove use and hygiene habits modify the associations of specific pesticides with Parkinson's disease. Environ. Int. 75, 144–150. https://doi.org/10.1016/j.envint.2014.11.002.

Gardner, R.C., Burke, J.F., Nettiksimmons, J., Goldman, S., Tanner, C.M., Yaffe, K., 2015. Traumatic brain injury in later life increases risk for Parkinson disease. Ann. Neurol. 77, 987–995. https://doi.org/10.1002/ana.24396.

Gatto, N.M., Cockburn, M., Bronstein, J., Manthripragada, A.D., Ritz, B., 2009. Wellwater consumption and Parkinson's disease in rural California. Environ. Health Perspect. 117, 1912–1918. https://doi.org/10.1289/ehp.0900852.

Gelb, D.J., Oliver, E., Gilman, S., 1999. Diagnostic criteria for Parkinson disease. Arch. Neurol. 56, 33–39.

Gintautas, P.A., Daniel, S.R., Macalady, D.L., 1992. Phenoxyalkanoic acid herbicides in municipal landfill leachates. Environ. Sci. Technol. 26, 517–521. https://doi.org/10.1021/es00027a011.

Goldman, S.M., Kamel, F., Ross, G.W., Bhudhikanok, G.S., Hoppin, J.A., Korell, M., Marras, C., Meng, C., Umbach, D.M., Kasten, M., Chade, A.R., Comyns, K., Richards, M.B., Sandler, D.P., Blair, A., Langston, J.W., Tanner, C.M., 2012. Genetic modification of the association of paraquat and Parkinson's disease. Mov. Disord. 27, 1652–1658. https://doi.org/10.1002/mds.25216.

Goldman, S.M., Musgrove, R.E., Jewell, S.A., Di Monte, D.A., 2017. Pesticides and Parkinson's disease: current experimental and epidemiological evidence. In: Aschner, M., Costa, L.G. (Eds.). Advances in Neurotoxicology. Environmental Factors in Neurodegenerative Diseases. Academic Press, Cambridge, MA, pp. 83–117.

Heltshe, S.L., Lubin, J.H., Koutros, S., Coble, J.B., Ji, B.T., Alavanja, M.C., Blair, A., Sandler, D.P., Hines, C.J., Thomas, K.W., Barker, J., Andreotti, G., Hoppin, J.A., Beane Freeman, L.E., 2012. Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study. J. Expo. Sci. Environ. Epidemiol. 22, 409–416. https://doi.org/10.1038/jes.2012.31.

Hernan, M.A., Takkouche, B., Caamano-Isorna, F., Gestal-Otero, J.J., 2002. A metaanalysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann. Neurol. 52, 276–284. https://doi.org/10.1002/ana.10277.

Hines, C.J., Deddens, J.A., Coble, J., Kamel, F., Alavanja, M.C., 2011. Determinants of captan air and dermal exposures among orchard pesticide applicators in the Agricultural Health Study. Ann. Occup. Hyg. 55, 620–633. https://doi.org/10.1093/annhyg/mer008.

Hirtz, D., Thurman, D.J., Gwinn-Hardy, K., Mohamed, M., Chaudhuri, A.R., Zalutsky, R., 2007. How common are the "common" neurologic disorders? Neurology 68, 326–337. https://doi.org/10.1212/01.wnl.0000252807.38124.a3.

Hoppin, J.A., Yucel, F., Dosemeci, M., Sandler, D.P., 2002. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the

Agricultural Health Study. J. Expo. Anal. Environ. Epidemiol. 12, 313–318. https://doi.org/10.1038/sj.jea.7500232.

Howe, C.J., Cole, S.R., Lau, B., Napravnik, S., Eron Jr., J.J., 2016. Selection bias due to loss to follow up in cohort studies. Epidemiology 27, 91–97. https://doi.org/10.1097/EDE.0000000000000409.

Hutson, C.B., Lazo, C.R., Mortazavi, F., Giza, C.C., Hovda, D., Chesselet, M.F., 2011. Traumatic brain injury in adult rats causes progressive nigrostriatal dopaminergic cell loss and enhanced vulnerability to the pesticide paraquat. J. Neurotrauma 28, 1783–1801. https://doi.org/10.1089/neu.2010.1723.

Jain, S., Himali, J., Beiser, A., Ton, T.G., Kelly-Hayes, M., Biggs, M.L., Delaney, J.A., Rosano, C., Seshadri, S., Frank, S.A., 2015. Validation of secondary data sources to identify Parkinson disease against clinical diagnostic criteria. Am. J. Epidemiol. 181, 185–190. https://doi.org/10.1093/aje/kwu326.

Jones, B.C., Huang, X., Mailman, R.B., Lu, L., Williams, R.W., 2014. The perplexing paradox of paraquat: the case for host-based susceptibility and postulated neurodegenerative effects. J. Biochem. Mol. Toxicol. 28, 191–197. https://doi.org/10.1002/jbt.21552.

Kamel, F., Tanner, C., Umbach, D., Hoppin, J., Alavanja, M., Blair, A., Comyns, K., Goldman, S., Korell, M., Langston, J., Ross, G., Sandler, D., 2007. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am. J. Epidemiol. 165, 364–374. https://doi.org/10.1093/aje/kwk024.

Kamel, F., Goldman, S.M., Umbach, D.M., Chen, H., Richardson, G., Barber, M.R., Meng, C., Marras, C., Korell, M., Kasten, M., Hoppin, J.A., Comyns, K., Chade, A., Blair, A., Bhudhikanok, G.S., Webster Ross, G., William Langston, J., Sandler, D.P., Tanner, C.M., 2014. Dietary fat intake, pesticide use, and Parkinson's disease. Park. Relat. Disord. 20, 82–87. https://doi.org/10.1016/j.parkreldis.2013.09.023.

Kanthasamy, A.G., Kitazawa, M., Kanthasamy, A., Anantharam, V., 2005. Dieldrininduced neurotoxicity: relevance to Parkinson's disease pathogenesis. Neurotoxicology 26, 701–719. https://doi.org/10.1016/j.neuro.2004.07.010.

Kenborg, L., Rugbjerg, K., Lee, P.C., Ravnskjaer, L., Christensen, J., Ritz, B., Lassen, C.F., 2015. Head injury and risk for Parkinson disease: results from a Danish case-control study. Neurology 84, 1098–1103. https://doi.org/10.1212/WNL.0000000000001362.

Kowal, S.L., Dall, T.M., Chakrabarti, R., Storm, M.V., Jain, A., 2013. The current and projected economic burden of Parkinson's disease in the United States. Mov. Disord. 28, 311–318. https://doi.org/10.1002/mds.25292.

Lee, P.C., Bordelon, Y., Bronstein, J., Ritz, B., 2012. Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease. Neurology 79, 2061–2066. https://doi.org/10.1212/WNL.0b013e3182703f0a28.

Lifshitz, J., Sullivan, P.G., Hovda, D.A., Wieloch, T., McIntosh, T.K., 2004. Mitochondrial damage and dysfunction in traumatic brain injury. Mitochondrion 4, 705–713. https://doi.org/10.1016/j.mito.2004.07.021.

Lilienfeld, D.E., Gallo, M.A., 1989. 2,4-D, 2,4,5-T, and 2,3,7,8-TCDD: an overview. Epidemiol. Rev. 11, 28–58. https://doi.org/10.1093/oxfordjournals.epirev.a036044.

Loane, D.J., Kumar, A., Stoica, B.A., Cabatbat, R., Faden, A.I., 2014. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. J. Neuropathol. Exp. Neurol. 73, 14–29. https://doi.org/10.1097/NEN.0000000000000021.

Narayan, S., Liew, Z., Paul, K., Lee, P.C., Sinsheimer, J.S., Bronstein, J.M., Ritz, B., 2013. Household organophosphorus pesticide use and Parkinson's disease. Int. J. Epidemiol. 42, 1476–1485. https://doi.org/10.1093/ije/dyt170.

Pezzoli, G., Cereda, E., 2013. Exposure to pesticides or solvents and risk of Parkinson disease. Neurology 80, 2035–2041. https://doi.org/10.1212/WNL.0b013e318294b3c8.

Ritz, B.R., Manthripragada, A.D., Costello, S., Lincoln, S.J., Farrer, M.J., Cockburn, M., Bronstein, J., 2009. Dopamine transporter genetic variants and pesticides in Parkinson's disease. Environ. Health Perspect. 117, 964–969. https://doi.org/10.1289/ehp.0800277.

Rothman, K.J., Greenland, S., Lash, T.L., 2008. Validity in epidemiologic studies. In: Rothman, K.J., Greenland, S., Lash, T.L. (Eds.), Modern Epidemiology. Lippincott Williams and Wilkins, Philadelphia, PA, pp. 128–147.

SAS Institute Inc, 2015. The PROC MIANALYZE Procedure. SAS/STAT 14.1 User's Guide. Cary, NC.

Shrestha, S., Parks, C.G., Keil, A.P., Umbach, D.M., Lerro, C.C., Lynch, C.F., Chen, H., Blair, A., Koutros, S., Hofmann, J.N., Beane Freeman, L.E., Sandler, D.P., 2019a. Overall and cause-specific mortality in a cohort of farmers and their spouses. Occup. Environ. Med. 76, 632–643. https://doi.org/10.1136/oemed-2019-105724.

Shrestha, S., Kamel, F., Umbach, D.M., Freeman, L.E.B., Koutros, S., Alavanja, M., Blair, A., Sandler, D.P., Chen, H., 2019b. High pesticide exposure events and olfactory impairment among U.S. Farmers. Environ. Health Perspect. 127, 17005. https://doi.org/10.1289/EHP3713.

Tanner, C.M., Ross, G.W., Jewell, S.A., Hauser, R.A., Jankovic, J., Factor, S.A., Bressman, S., Deligtisch, A., Marras, C., Lyons, K.E., Bhudhikanok, G.S., Roucoux, D. F., Meng, C., Abbott, R.D., Langston, J.W., 2009. Occupation and risk of parkinsonism: a multicenter case-control study. Arch. Neurol. 66, 1106–1113. https://doi.org/10.1001/archneurol.2009.195.

Tanner, C.M., Kamel, F., Ross, G.W., Hoppin, J.A., Goldman, S.M., Korell, M., Marras, C., Bhudhikanok, G.S., Kasten, M., Chade, A.R., Comyns, K., Richards, M.B., Meng, C., Priestley, B., Fernandez, H.H., Cambi, F., Umbach, D.M., Blair, A., Sandler, D.P., Langston, J.W., 2011. Rotenone, paraquat, and Parkinson's disease. Environ. Health Perspect. 119, 866–872. https://doi.org/10.1289/ehp.1002839.

Taylor, K.M., Saint-Hilaire, M.H., Sudarsky, L., Simon, D.K., Hersh, B., Sparrow, D., Hu, H., Weisskopf, M.G., 2016. Head injury at early ages is associated with risk of Parkinson's disease. Park. Relat. Disord. 23, 57–61. https://doi.org/10.1016/j.parkreldis.2015.12.005.

Terry Jr., A.V., 2012. Functional consequences of repeated organophosphate exposure: potential non-cholinergic mechanisms. Pharmacol. Ther. 134, 355–365. https://doi.org/10.1016/j.pharmthera.2012.03.001.

Thomas, K.W., Dosemeci, M., Hoppin, J.A., Sheldon, L.S., Croghan, C.W., Gordon, S.M., Jones, M.L., Reynolds, S.J., Raymer, J.H., Akland, G.G., Lynch, C.F., Knott, C.E., Sandler, D.P., Blair, A.E., Alavanja, M.C., 2010. Urinary biomarker, dermal, and air measurement results for 2,4-D and chlorpyrifos farm applicators in the Agricultural Health Study. J. Expo. Sci. Environ. Epidemiol. 20, 119–134. https://doi.org/10.1038/jes.2009.6.

US Administration on Aging, 2012. A Profile of Older Americans: 2012. US Administration on Aging.

Uversky, V.N., Li, J., Bower, K., Fink, A.L., 2002. Synergistic effects of pesticides and metals on the fibrillation of alpha-synuclein: implications for Parkinson's disease. Neurotoxicology 23, 527–536.

van der Mark, M., Brouwer, M., Kromhout, H., Nijssen, P., Huss, A., Vermeulen, R., 2012. Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. Environ. Health Perspect. 120, 340–347. https://doi.org/10.1289/ehp.1103881.

van der Mark, M., Vermeulen, R., Nijssen, P.C., Mulleners, W.M., Sas, A.M., van Laar, T., Brouwer, M., Huss, A., Kromhout, H., 2014. Occupational exposure to pesticides and endotoxin and Parkinson disease in The Netherlands. Occup. Environ. Med. 71, 757–764. https://doi.org/10.1136/oemed-2014-102170.

Wang, A., Cockburn, M., Ly, T.T., Bronstein, J.M., Ritz, B., 2014. The association between ambient exposure to organophosphates and Parkinson's disease risk. Occup. Environ. Med. 71, 275–281. https://doi.org/10.1136/oemed-2013-101394.

Ware, G.W., 1988. Silvex (2,4,5-TP). In: Ware, G.W. (Ed.), Rev Environ Contam Toxicol. Reviews of Environmental Contamination and Toxicology, vol. 104. Springer, New York, NY, pp. 195–202.

Weisskopf, M.G., Knekt, P., O'Reilly, E.J., Lyytinen, J., Reunanen, A., Laden, F., Altshul, L., Ascherio, A., 2010. Persistent organochlorine pesticides in serum and risk of Parkinson disease. Neurology 74, 1055–1061. https://doi.org/10.1212/WNL.0b013e3181d76a93.

Supplemental Figure 1: Timeline of the Agricultural Health Study

Applicators			

Enrollment questionnaire (n=52,394)
    Ever never use of 50 pesticides
    Duration and frequency of 22 pesticides
Take home questionnaire (n=22,916)
    Duration and frequency of 28 pesticides
    Ever use of "other" pesticides
	Completed by 33,456 applicators
	Participants provided names of pesticides
	they used in the last year or the most recent
	year pesticides were used
		Completed by 24,170 applicators	Completed by 24,145
			applicators

Spouses			
Enrollment (n=32,345) Ever use of 50 pesticides	Completed by 23,796 spouses Participants provided names of pesticides they used in the last year or the most recent year pesticides were used	Completed by 19,959 spouses	Completed by 18,186 spouses

1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017

Phase 1   Phase 2   Phase 3   Phase 4

Farming and Movement Evaluation (FAME)   PD validation/confirmation effort

Mortality follow up

1

Supplemental Figure 2: Selection of Parkinson's disease cases from a pool of incident potential cases

Incident potential PD cases (n=598)
Phase 2 self-report (n=59)
FAME after Phase 2 (n=12)
Phase 3 self-report (n=139)
Phase 4 self-report (n=341)
Other sources (n=16)
Death certificates (n=31)

Validation screener obtained for 440 participants

Incident PD with screener (n=440)
Phase 2 self-report (n=32)
FAME after Phase 2 (n=5)
Phase 3 self-report (n=102)
Phase 4 self-report (n=259)
Other sources (n=11)
Death certificates (n=31)

379 confirmed by screener evaluation

PD classification based on screener

Possible/probable PD (n=342)	53 cases were confirmed PD and 4 deemed questionable by MR [26 cases were confirmed PD in FAME]
Questionable (n=18)	1 case confirmed PD by MR
Other (n=38)	1 case confirmed PD and 1 deemed questionable by MR [2 cases were confirmed PD in FAME]
No PD (n=41)	[1 case was confirmed PD in FAME]

Incident potential PD without screener (n=158)
Phase 2 self-report (n=22)
FAME after Phase 2 (n=7)
Phase 3 self-report (n=34)
Phase 4 self-report (n=82)
Other sources (n=5)
(n=22 confirmed by FAME; death certificate on PD for 33)

8 providing inconsistent responses excluded from analysis

Incident PD (n=491; 341 with some confirmation data from screener and 150 without confirmation from screener)

Those with no conflicting information across data sources (screener, MR, FAME) included in analysis (n=341)

Of the 491, [341 + 22 (FAME confirmed without screener) + 33 (death certificate without screener) = 396 (80.6% had some supporting information from other sources)

Abbreviations: PD, Parkinson's disease; FAME, Farming and Movement Evaluation Study; MR, Medical Record

2

Supplemental Table 1: Ever-use of any pesticides reported at enrollment and PD risk in male pesticide applicators and female spouses

	Lifetime days[b]	Incident case analysis (n=66,110)			Overall (incident and prevalent) case analysis (n=66,216)[a]	
		No PD (n(%))	PD (n(%))	HR (95% CI)[c]	PD (n(%))	OR (95% CI)[d]
Overall sample[e]	Never use	11945 (19.7)	40 (8.8)	Ref	56 (10)	Ref
	> 0 to 39	12386 (20.4)	82 (18)	1.23 (0.81, 1.89)	106 (19)	1.18 (0.81, 1.71)
	40 to 179	14415 (23.8)	128 (28.1)	1.21 (0.79, 1.86)	147 (26.3)	1.07 (0.73, 1.56)
	180 to 370	10668 (17.6)	104 (22.8)	1.27 (0.82, 1.98)	122 (21.9)	1.16 (0.79, 1.72)
	> 370	11240 (18.5)	102 (22.4)	1.07 (0.69, 1.67)	127 (22.8)	1.06 (0.72, 1.57)
Male applicators only[f]	0 to 64	9984 (27.2)	106 (28.6)	Ref	133 (29.7)	Ref
	65 to 225	11644 (31.8)	101 (27.3)	0.86 (0.65, 1.13)	118 (26.3)	0.83 (0.64, 1.07)
	226 to 458	7689 (21)	81 (21.9)	0.98 (0.73, 1.31)	93 (20.8)	0.96 (0.73, 1.26)
	> 458	7328 (20)	82 (22.2)	0.79 (0.59, 1.06)	104 (23.2)	0.88 (0.67, 1.14)
Female spouses only[g]	Never use	11360 (49.7)	38 (45.8)	Ref	51 (48.1)	Ref
	> 0 to 51	6047 (26.4)	8 (9.6)	0.47 (0.22, 1.02)	13 (12.3)	0.63 (0.34, 1.16)
	> 51	5472 (23.9)	37 (44.6)	1.58 (1.00, 2.50)	42 (39.6)	1.48 (0.98, 2.25)

Abbreviation: CI, Confidence Intervals; HR, Hazard Ratio; OR, Odds Ratio; PD, Parkinson's disease
[a]Includes prevalent cases
[b]Life time days calculated from questions on general pesticide use at Phase 1 enrollment questionnaire (how many years did you personally mix or apply pesticides? And during those years, how many days per year did you personally mix or apply pesticides?)
[c]HR adjusted for state of residence, smoking status, education
[d]OR adjusted for age at enrollment, state of residence, smoking status, education
[e]In the overall sample, quartiles of lifetime days of use of any pesticide among users were compared with never use as the referent
[f]Among male applicators, higher quartiles of lifetime days of any pesticide use were compared with the lowest quartile (note: never use was not chosen as the referent because only a few participants indicated so)
[g]Among female spouses, median lifetime days of use of any pesticide among users were compared with never use as the referent

Supplemental Table 2: Ever-use of pesticides reported at enrollment and Parkinson's disease (PD) risk in male pesticide applicators and female spouses

Pesticide	Male applicators (n=37,284)			Female spouses (n=27,673)		
	non-PD, n(%)	PD, n (%)	HR (95% CI)[a]	non-PD , n (%)	PD, n (%)	HR (95% CI)[a]
Organochlorine insecticide						
Aldrin ($\leq$ 63y)[b]	1472 (8.4)	14 (16.7)	0.86 (0.46, 1.60)			
> 63y	4839 (33)	82 (36.4)	0.92 (0.66, 1.28)			
Chlordane	8777 (26.7)	122 (38.4)	1.00 (0.78, 1.28)	*1142 (4.4)*	*6 (5.8)*	*0.85 (0.37, 1.94)*
Dieldrin	2333 (7.2)	37 (12)	0.86 (0.58, 1.28)			
DDT	8238 (25.2)	139 (44.3)	0.90 (0.69, 1.17)	977 (3.8)	6 (5.8)	0.77 (0.34, 1.77)
Heptachlor	5291 (16.4)	87 (28.2)	1.09 (0.80, 1.48)			
Toxaphene	5028 (15.3)	60 (19.1)	0.78 (0.59, 1.04)			
Lindane	6730 (20.4)	73 (23.3)	0.94 (0.72, 1.23)			
Carbamate insecticide						
Aldicarb	3662 (11.3)	27 (8.7)	0.94 (0.61, 1.46)			
Carbaryl	18622 (56.5)	194 (62.4)	1.10 (0.85, 1.43)	8287 (31.6)	36 (34)	1.00 (0.63, 1.59)
Carbofuran	9602 (28.8)	113 (36.1)	1.09 (0.86, 1.37)			
Organophosphate insecticide						
Chlorpyrifos	15434 (42.9)	139 (38.3)	0.93 (0.75, 1.16)			
Coumaphos	3005 (9.2)	32 (10.5)	1.00 (0.69, 1.44)			
Diazinon	10821 (32.8)	97 (31.2)	0.75 (0.58, 0.98)	2783 (10.7)	7 (6.7)	0.57 (0.27, 1.24)
Dichlorvos	3662 (11)	42 (13.7)	1.08 (0.78, 1.51)			
Fonofos	7634 (22.8)	73 (23.2)	0.94 (0.71, 1.23)			
Malathion	24541 (72)	253 (76.7)	1.05 (0.81, 1.35)	5274 (20.1)	23 (21.7)	0.90 (0.53, 1.54)
Parathion	5323 (16.2)	61 (19.5)	0.97 (0.73, 1.3)			
Phorate	11414 (34.5)	120 (38)	0.97 (0.76, 1.24)			
Terbufos	13656 (40.7)	145 (46.2)	1.3 (1.03, 1.64)			
Permethrin insecticide						
Permethrin (Crops) ($\leq$ 63y)[b]	2842 (16)	8 (9.9)	0.6 (0.29, 1.24)			
> 63y	1764 (11.5)	26 (11.7)	1.2 (0.79, 1.81)			
Permethrin (Animals)	4665 (13.9)	36 (11.7)	1.03 (0.72, 1.47)			
Fumigant						
Carbon disulfide/ Carbon tetrachloride	1922 (5.8)	29 (9.2)	1.01 (0.69, 1.49)			
Aluminum phosphide	*1657 (5)*	*15 (4.8)*	*1.01 (0.6, 1.7)*			
Ethylene dibromide	1243 (3.8)	5 (1.6)	0.34 (0.14, 0.83)			
Methyl bromide	5248 (15.7)	46 (14.4)	0.85 (0.58, 1.25)			

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Fungicide

Benomyl[c]	*3147 (9.8)*	*25 (8.2)*	*0.74 (0.44, 1.23)*		
Captan	3897 (11.8)	33 (10.7)	0.91 (0.63, 1.31)		
Chlorothalonil	2552 (7.7)	21 (6.7)	1.02 (0.61, 1.69)		
Maneb (≤ 63y)[b]	1493 (8.4)	8 (9.3)	1.46 (0.64, 3.33)		
> 63y	1696 (11.1)	21 (9.3)	0.81 (0.48, 1.37)		
Metalaxyl	7885 (23.7)	65 (20.3)	0.88 (0.64, 1.21)		
Herbicide					
Alachlor	18551 (55)	189 (59.6)	1.08 (0.86, 1.35)	1107 (4.3)	6 (5.8)	1.06 (0.32, 3.53)
Butylate	10877 (33.2)	108 (35)	1.06 (0.82, 1.37)		
Chlorimuron ethyl	12715 (38.5)	105 (33.2)	1.02 (0.80, 1.29)		
Dicamba	17238 (52.8)	160 (53)	0.96 (0.74, 1.26)		
EPTC	6840 (20.7)	53 (17.5)	0.85 (0.63, 1.16)		
Glyphosate	27733 (76.9)	278 (76.2)	1.02 (0.79, 1.30)	8867 (34)	42 (39.6)	1.44 (0.92, 2.25)
Imazethapyr	14643 (44.9)	128 (42.4)	1.11 (0.85, 1.45)	769 (3)	4 (3.9)	1.15 (0.28, 4.72)
Metolachlor	16054 (47.7)	127 (41)	0.81 (0.64, 1.03)	862 (3.3)	5 (4.8)	1.29 (0.36, 4.67)
Paraquat	8103 (24.5)	84 (26.3)	1.04 (0.79, 1.35)		
Pendimethalin	15267 (45.9)	135 (42.6)	1.03 (0.83, 1.29)		
Petroleum distillate	16240 (49.4)	154 (49)	0.99 (0.79, 1.24)		
Trifluralin	17624 (54.9)	182 (61.1)	1.36 (1.04, 1.78)	1339 (5.2)	8 (7.8)	1.42 (0.53, 3.77)
2,4-D	27778 (77.3)	289 (79.8)	1.02 (0.78, 1.33)	3955 (15.2)	21 (19.8)	0.98 (0.56, 1.71)
2,4,5-T	7256 (22.3)	117 (37.5)	1.53 (1.20, 1.97)		
2,4,5-TP	3181 (9.8)	23 (7.4)	0.39 (0.25, 0.61)		
Atrazine	26301 (73)	268 (73.6)	1.05 (0.82, 1.33)	1172 (4.5)	5 (4.8)	0.46 (0.13, 1.67)
Cyanazine	14546 (43.3)	136 (43.7)	0.96 (0.75, 1.22)	744 (2.9)	6 (5.8)	2.80 (0.79, 9.95)
Metribuzin	15192 (47.9)	137 (46.9)	0.86 (0.65, 1.13)		

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; HR, Hazard Ratio

[a]HR adjusted for state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide)

[b]Hazard ratio allowed to vary by the median age (i.e., 63 years) for pesticides that did not meet proportional hazards assumptions (p ≤ 0.10)

[c]Proportional hazards assumptions not met for those in italics, but there was no adequate sample size to provide stratified estimates by the median age

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Supplemental Table 3: Ever-use of pesticides reported at enrollment and incident PD in all participants
Stratified by follow-up period (≤ 10 years versus > 10 years)

| Pesticide | Hazard ratio (95% CI) | | p-heterogeneity |
	Follow up ≤ 10y	Follow up > 10 y	
Organochlorine insecticide			
Aldrin	0.94 (0.64, 1.38)	0.89 (0.63, 1.26)	0.78
Chlordane	1.14 (0.83, 1.57)	0.98 (0.73, 1.32)	0.42
Dieldrin	0.74 (0.42, 1.31)	1.00 (0.63, 1.58)	0.39
DDT	0.94 (0.69, 1.28)	0.80 (0.58, 1.08)	0.34
Heptachlor	1.07 (0.72, 1.58)	0.97 (0.68, 1.39)	0.67
Toxaphene	0.90 (0.60, 1.35)	0.73 (0.50, 1.08)	0.44
Lindane	0.95 (0.65, 1.38)	0.90 (0.65, 1.25)	0.84
Carbamate insecticide			
Aldicarb	0.92 (0.47, 1.78)	1.15 (0.69, 1.91)	0.58
Carbaryl	1.22 (0.93, 1.60)	1.00 (0.77, 1.30)	0.14
Carbofuran	1.00 (0.72, 1.39)	0.91 (0.68, 1.22)	0.63
Organophosphate insecticide			
Chlorpyrifos	0.92 (0.69, 1.24)	0.91 (0.71, 1.17)	0.94
Coumaphos	1.20 (0.72, 1.98)	0.93 (0.58, 1.48)	0.46
Diazinon	0.77 (0.56, 1.08)	0.71 (0.53, 0.95)	0.66
Dichlorvos	1.17 (0.73, 1.87)	1.09 (0.74, 1.61)	0.82
Fonofos	1.04 (0.72, 1.50)	0.83 (0.59, 1.16)	0.33
Malathion	1.14 (0.85, 1.53)	0.92 (0.69, 1.21)	0.09
Parathion	1.17 (0.80, 1.71)	0.84 (0.58, 1.23)	0.20
Phorate	0.93 (0.67, 1.30)	0.80 (0.59, 1.09)	0.44
Terbufos	1.39 (1.01, 1.91)	1.25 (0.94, 1.67)	0.56
Permethrin insecticide			
Permethrin (Crops)	0.98 (0.57, 1.67)	0.99 (0.64, 1.53)	0.96
Permethrin (Animals)	0.95 (0.54, 1.66)	1.13 (0.77, 1.67)	0.60
Fumigant			
Carbon disulfide/Carbon tetrachloride	0.82 (0.45, 1.49)	1.21 (0.77, 1.92)	0.29
Aluminum phosphide	1.25 (0.59, 2.66)	0.97 (0.50, 1.89)	0.61
Methyl bromide	1.00 (0.62, 1.60)	0.75 (0.47, 1.21)	0.34
Fungicide			
Benomyl	0.86 (0.45, 1.64)	0.75 (0.41, 1.39)	0.73
Captan	0.73 (0.41, 1.31)	0.91 (0.59, 1.43)	0.54
Chlorothalonil	1.04 (0.53, 2.05)	0.91 (0.48, 1.74)	0.76
Maneb	0.90 (0.49, 1.64)	0.84 (0.48, 1.46)	0.86
Metalaxyl	0.97 (0.63, 1.51)	0.76 (0.51, 1.15)	0.36
Herbicide			
Alachlor	1.34 (0.99, 1.79)	0.98 (0.74, 1.31)	0.04
Butylate	1.37 (0.99, 1.90)	0.75 (0.53, 1.05)	0.003
Chlorimuron ethyl	1.38 (0.99, 1.92)	0.83 (0.60, 1.16)	0.01
Dicamba	1.11 (0.81, 1.53)	0.82 (0.60, 1.11)	0.06
EPTC	1.08 (0.71, 1.64)	0.68 (0.45, 1.04)	0.10
Glyphosate	1.22 (0.93, 1.61)	1.02 (0.79, 1.32)	0.14
Imazethapyr	1.23 (0.88, 1.73)	0.92 (0.67, 1.27)	0.11
Metolachlor	1.00 (0.73, 1.37)	0.67 (0.49, 0.91)	0.03
Paraquat	1.21 (0.86, 1.72)	1.00 (0.73, 1.39)	0.38
Pendimethalin	1.20 (0.87, 1.65)	0.98 (0.73, 1.32)	0.28

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Petroleum distillate	1.06 (0.79, 1.44)	0.84 (0.64, 1.12)	0.17
Trifluralin	1.61 (1.18, 2.20)	1.08 (0.79, 1.47)	0.01
2,4-D	1.21 (0.88, 1.68)	0.95 (0.69, 1.31)	0.06
2,4,5-T	1.77 (1.28, 2.45)	1.42 (1.04, 1.95)	0.25
2,4,5-TP	0.33 (0.16, 0.68)	0.44 (0.26, 0.75)	0.52
Atrazine	1.23 (0.89, 1.69)	0.90 (0.66, 1.24)	0.02
Cyanazine	1.05 (0.76, 1.45)	0.81 (0.59, 1.10)	0.14
Metribuzin	0.97 (0.69, 1.37)	0.79 (0.57, 1.09)	0.24

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; PD, Parkinson's disease
HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide)

Supplemental Table 4: Ever-use of pesticides reported at enrollment and PD in all participants including prevalent cases (n=66,216)

Pesticide	non-PD, n (%)	PD, n (%)	OR (95% CI)[a]
Organochlorine insecticide			
Aldrin	6507 (11.1)	123 (24.6)	1.01 (0.76, 1.33)
Chlordane	9758 (16.5)	147 (29)	1.01 (0.8, 1.28)
Dieldrin	2440 (4.1)	50 (10)	0.92 (0.65, 1.29)
DDT	8954 (15.4)	175 (35.4)	0.9 (0.7, 1.14)
Heptachlor	5442 (9.4)	105 (21.3)	0.99 (0.74, 1.31)
Toxaphene	5160 (8.7)	65 (12.9)	0.74 (0.56, 0.98)
Lindane	7250 (12.1)	94 (18.5)	1.03 (0.81, 1.3)
Carbamate insecticide			
Aldicarb	3809 (6.5)	32 (6.5)	1.02 (0.68, 1.53)
Carbaryl	27180 (45.5)	272 (53.9)	1.06 (0.86, 1.31)
Carbofuran	10017 (16.7)	134 (26.4)	1.01 (0.81, 1.26)
Organophosphate insecticide			
Chlorpyrifos	16700 (26.8)	175 (30.9)	0.99 (0.82, 1.21)
Coumaphos	3423 (5.7)	41 (8.1)	1.08 (0.78, 1.5)
Diazinon	13979 (23.3)	132 (26)	0.85 (0.68, 1.06)
Dichlorvos	4425 (7.3)	53 (10.4)	1.14 (0.85, 1.54)
Fonofos	8219 (13.6)	89 (17.1)	0.9 (0.7, 1.15)
Malathion	28496 (48.7)	302 (61.9)	1.06 (0.84, 1.34)
Parathion	5661 (9.5)	76 (15)	1.07 (0.82, 1.39)
Phorate	11404 (19.9)	134 (28.5)	0.87 (0.69, 1.11)
Terbufos	13718 (23.8)	159 (33.5)	1.21 (0.96, 1.52)
Permethrin insecticide			
Permethrin (Crops)	5263 (8.8)	43 (8.5)	1.00 (0.73, 1.39)
Permethrin (Animals)	5696 (9.4)	45 (8.8)	1.05 (0.76, 1.44)
Fumigant			
Carbon disulfide/Carbon tetrachloride	2099 (3.5)	40 (7.7)	1.08 (0.77, 1.51)
Aluminum phosphide	1707 (2.8)	22 (4.3)	1.4 (0.9, 2.16)
Ethylene dibromide	1294 (2.2)	9 (1.8)	0.56 (0.29, 1.09)
Methyl bromide	5707 (9.5)	54 (10.5)	0.9 (0.63, 1.27)
Fungicide			
Benomyl	3492 (6)	34 (7)	0.89 (0.57, 1.4)
Captan	4617 (7.7)	39 (7.7)	0.81 (0.58, 1.14)
Chlorothalonil	2899 (4.8)	26 (5.1)	0.95 (0.6, 1.5)
Maneb	3715 (6.2)	37 (7.3)	0.95 (0.63, 1.42)
Metalaxyl	7968 (13.6)	68 (13.8)	0.89 (0.65, 1.21)
Herbicide			
Alachlor	19057 (32.1)	223 (44.8)	1.16 (0.92, 1.46)
Butylate	10995 (19)	118 (25.1)	0.97 (0.75, 1.24)
Chlorimuron	12693 (21.8)	122 (25.5)	1.1 (0.86, 1.41)
Dicamba	17945 (31)	190 (40.3)	0.95 (0.74, 1.21)
EPTC	7049 (12.2)	62 (13.2)	0.8 (0.6, 1.08)
Glyphosate	35406 (58.6)	343 (65.7)	1.08 (0.87, 1.34)
Imazethapyr	15124 (26.3)	148 (31.6)	0.99 (0.76, 1.27)
Metolachlor	16114 (27.9)	153 (32.4)	0.84 (0.66, 1.06)
Paraquat	8526 (14.2)	103 (20.1)	1.13 (0.89, 1.44)
Pendimethalin	15250 (26.1)	155 (32.2)	1.14 (0.91, 1.45)

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Petroleum distillates	16756 (28.9)	167 (35)	0.87 (0.69, 1.08)
Trifluralin	18665 (32.2)	216 (46)	1.28 (0.99, 1.64)
2,4-D	28871 (49.8)	313 (65.8)	1.07 (0.82, 1.41)
2,4,5-T	7264 (12.5)	134 (27.1)	1.41 (1.1, 1.8)
2,4,5-TP	3287 (5.5)	29 (5.7)	0.46 (0.3, 0.69)
Atrazine	25297 (42.8)	280 (56.7)	0.96 (0.73, 1.25)
Cyanazine	14641 (25.2)	165 (34.5)	1.01 (0.79, 1.29)
Metribuzin	15500 (26.8)	164 (35.1)	0.92 (0.71, 1.19)

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; OR, Odds Ratio

[a]OR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation $\geq$ 0.40 with the ever-use variable of the target pesticide)

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Supplemental Table 5: Intensity-weighted lifetime days of pesticide use reported at enrollment and PD in male applicators (including prevalent cases, n = 37,362)

Pesticide	Lifetime days	No PD (n (%))	PD (n (%))	OR (95 % CI)
Organochlorine insecticide				
Aldrin	Never use	13397 (82.7)	171 (75)	Ref
	Tertile 1	992 (6.1)	20 (8.8)	0.82 (0.49, 1.35)
	Tertile 2	908 (5.6)	19 (8.3)	0.81 (0.48, 1.37)
	Tertile 3	900 (5.6)	18 (7.9)	0.73 (0.42, 1.25)
Chlordane	Never use	13296 (80.9)	177 (75.3)	Ref
	Tertile 1	1063 (6.5)	19 (8.1)	0.94 (0.57, 1.53)
	Tertile 2	1077 (6.6)	17 (7.2)	0.78 (0.46, 1.30)
	Tertile 3	999 (6.1)	22 (9.4)	0.99 (0.62, 1.58)
Dieldrin	Never use	15739 (96.2)	217 (93.5)	Ref
	≤ Median	307 (1.9)	9 (3.9)	0.97 (0.48, 1.97)
	> Median	308 (1.9)	6 (2.6)	0.66 (0.28, 1.53)
DDT	Never use	12677 (78.6)	137 (59.8)	Ref
	Tertile 1	1192 (7.4)	26 (11.4)	0.87 (0.55, 1.37)
	Tertile 2	1133 (7)	41 (17.9)	1.39 (0.93, 2.06)
	Tertile 3	1118 (6.9)	25 (10.9)	0.9 (0.56, 1.43)
Heptachlor	Never use	14194 (87.4)	183 (78.9)	Ref
	Tertile 1	670 (4.1)	16 (6.9)	1.21 (0.70, 2.11)
	Tertile 2	715 (4.4)	19 (8.2)	1.34 (0.80, 2.24)
	Tertile 3	653 (4)	14 (6)	1.03 (0.57, 1.85)
Toxaphene	Never use	14905 (88.5)	217 (89.3)	Ref
	Tertile 1	690 (4.1)	8 (3.3)	0.56 (0.27, 1.14)
	Tertile 2	637 (3.8)	10 (4.1)	0.75 (0.39, 1.43)
	Tertile 3	614 (3.6)	8 (3.3)	0.56 (0.27, 1.16)
Lindane	Never use	15591 (86.3)	231 (86.2)	Ref
	Tertile 1	823 (4.6)	8 (3)	0.57 (0.28, 1.17)
	Tertile 2	839 (4.6)	19 (7.1)	1.3 (0.8, 2.1)
	Tertile 3	815 (4.5)	10 (3.7)	0.73 (0.39, 1.39)
Carbamate insecticide				
Carbaryl	Never use	9518 (57.9)	137 (58.5)	Ref
	Tertile 1	2426 (14.8)	34 (14.5)	0.81 (0.55, 1.2)
	Tertile 2	2391 (14.5)	32 (13.7)	0.7 (0.46, 1.07)
	Tertile 3	2099 (12.8)	31 (13.2)	0.62 (0.38, 1)
Carbofuran	Never use	23484 (72)	240 (65.6)	Ref
	Tertile 1	3025 (9.3)	47 (12.8)	1.18 (0.85, 1.64)
	Tertile 2	3095 (9.5)	47 (12.8)	1.13 (0.81, 1.56)
	Tertile 3	2998 (9.2)	32 (8.7)	0.81 (0.55, 1.19)
Organophosphate insecticide				
Chlorpyrifos	Never use	18439 (54.9)	223 (57.3)	Ref
	Tertile 1	4991 (14.9)	62 (15.9)	1.17 (0.88, 1.56)
	Tertile 2	5152 (15.3)	45 (11.6)	0.81 (0.58, 1.12)
	Tertile 3	4982 (14.8)	59 (15.2)	1.19 (0.89, 1.60)
Coumaphos	Never use	29725 (91.2)	333 (90.5)	Ref
	Tertile 1	955 (2.9)	11 (3)	0.95 (0.52, 1.75)
	Tertile 2	979 (3)	13 (3.5)	1.11 (0.63, 1.94)
	Tertile 3	938 (2.9)	11 (3)	1 (0.54, 1.84)
Diazinon	Never use	13412 (79.2)	192 (79.7)	Ref

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	Tertile 1	1194 (7.1)	17 (7.1)	0.92 (0.55, 1.53)
	Tertile 2	1209 (7.1)	20 (8.3)	1 (0.62, 1.62)
	Tertile 3	1120 (6.6)	12 (5)	0.67 (0.36, 1.22)
Dichlorvos	Never use	29516 (89.2)	324 (87.3)	Ref
	Tertile 1	1182 (3.6)	8 (2.2)	0.57 (0.28, 1.15)
	Tertile 2	1205 (3.6)	23 (6.2)	1.72 (1.11, 2.66)
	Tertile 3	1169 (3.5)	16 (4.3)	1.21 (0.72, 2.02)
Fonofos	Never use	25838 (77.6)	296 (78.3)	Ref
	Tertile 1	2467 (7.4)	27 (7.1)	0.93 (0.62, 1.4)
	Tertile 2	2526 (7.6)	32 (8.5)	1.05 (0.72, 1.53)
	Tertile 3	2463 (7.4)	23 (6.1)	0.74 (0.48, 1.15)
Malathion	Never use	5557 (34.5)	78 (34.8)	Ref
	Tertile 1	3547 (22)	51 (22.8)	1.01 (0.7, 1.47)
	Tertile 2	3645 (22.6)	45 (20.1)	0.85 (0.57, 1.24)
	Tertile 3	3359 (20.9)	50 (22.3)	0.89 (0.6, 1.3)
Parathion	Never use	16605 (92.1)	245 (91.1)	Ref
	≤ Median	718 (4)	12 (4.5)	0.93 (0.51, 1.68)
	> Median	697 (3.9)	12 (4.5)	0.98 (0.54, 1.79)
Phorate	Never use	10665 (67.6)	134 (61.5)	Ref
	Tertile 1	1713 (10.9)	28 (12.8)	1.07 (0.69, 1.66)
	Tertile 2	1755 (11.1)	37 (17)	1.4 (0.94, 2.08)
	Tertile 3	1640 (10.4)	19 (8.7)	0.72 (0.43, 1.19)
Terbufos	Never use	18415 (59.4)	192 (56.1)	Ref
	Tertile 1	4184 (13.5)	46 (13.5)	1.18 (0.84, 1.66)
	Tertile 2	4293 (13.8)	60 (17.5)	1.44 (1.06, 1.97)
	Tertile 3	4108 (13.3)	44 (12.9)	1.13 (0.79, 1.6)
Permethrin insecticide				
Permethrin (Crops)	Never use	28383 (86.5)	328 (89.4)	Ref
	Tertile 1	1470 (4.5)	19 (5.2)	1.46 (0.91, 2.34)
	Tertile 2	1492 (4.5)	12 (3.3)	0.94 (0.52, 1.69)
	Tertile 3	1466 (4.5)	8 (2.2)	0.66 (0.32, 1.35)
Permethrin (Animals)	Never use	28783 (86.3)	336 (89.6)	Ref
	Tertile 1	1574 (4.7)	11 (2.9)	0.82 (0.45, 1.52)
	Tertile 2	1508 (4.5)	10 (2.7)	0.79 (0.41, 1.49)
	Tertile 3	1490 (4.5)	18 (4.8)	1.52 (0.93, 2.46)
Fumigant				
Carbon disulphide/Carbon tetrachloride	Never use	17467 (95.8)	250 (94)	Ref
	≤ Median	398 (2.2)	7 (2.6)	0.74 (0.34, 1.6)
	> Median	364 (2)	9 (3.4)	1.08 (0.55, 2.14)
Ethylene Dibromide	Never use	17442 (95.6)	258 (95.2)	Ref
	≤ Median	397 (2.2)	8 (3)	1.3 (0.63, 2.71)
	> Median	411 (2.3)	5 (1.8)	0.76 (0.31, 1.9)
Methyl Bromide	Never use	28072 (84.9)	328 (86.1)	Ref
	Tertile 1	1613 (4.9)	15 (3.9)	0.81 (0.47, 1.41)
	Tertile 2	1670 (5.1)	23 (6)	1.31 (0.8, 2.12)
	Tertile 3	1706 (5.2)	15 (3.9)	0.77 (0.43, 1.37)
Fungicide				
Benomyl	Never use	14990 (92.8)	206 (91.2)	Ref
	≤ Median	592 (3.7)	5 (2.2)	0.53 (0.21, 1.37)
	> Median	573 (3.5)	15 (6.6)	1.48 (0.77, 2.83)

Captan	Never use	29167 (89.8)	334 (91.5)	Ref
	Tertile 1	1224 (3.8)	9 (2.5)	0.69 (0.35, 1.36)
	Tertile 2	1046 (3.2)	6 (1.6)	0.54 (0.24, 1.21)
	Tertile 3	1060 (3.3)	16 (4.4)	1.21 (0.72, 2.04)
Chlorothalonil	Never use	30547 (92.8)	351 (94.4)	Ref
	Tertile 1	750 (2.3)	8 (2.2)	0.98 (0.47, 2.04)
	Tertile 2	787 (2.4)	8 (2.2)	1.01 (0.47, 2.15)
	Tertile 3	816 (2.5)	5 (1.3)	0.69 (0.27, 1.76)
Maneb/Mancozeb	Never use	15485 (92.5)	224 (93.3)	Ref
	Tertile 1	422 (2.5)	5 (2.1)	0.61 (0.24, 1.52)
	Tertile 2	428 (2.6)	5 (2.1)	0.58 (0.23, 1.47)
	Tertile 3	399 (2.4)	6 (2.5)	0.68 (0.28, 1.62)
Metalaxyl	Never use	13387 (82.1)	193 (83.5)	Ref
	Tertile 1	986 (6)	17 (7.4)	1.31 (0.78, 2.18)
	Tertile 2	1005 (6.2)	15 (6.5)	1.31 (0.73, 2.36)
	Tertile 3	936 (5.7)	6 (2.6)	0.67 (0.28, 1.61)
Herbicide				
Alachlor	Never use	14805 (46.3)	150 (42.3)	Ref
	Tertile 1	5731 (17.9)	72 (20.3)	1.19 (0.88, 1.62)
	Tertile 2	5827 (18.2)	67 (18.9)	1.12 (0.82, 1.54)
	Tertile 3	5641 (17.6)	66 (18.6)	1.2 (0.87, 1.65)
Butylate	Never use	11339 (71.3)	163 (74.8)	Ref
	Tertile 1	1520 (9.6)	25 (11.5)	1.18 (0.75, 1.85)
	Tertile 2	1564 (9.8)	15 (6.9)	0.7 (0.4, 1.22)
	Tertile 3	1477 (9.3)	15 (6.9)	0.76 (0.44, 1.33)
Chlorimuron Ethyl	Never use	10728 (67)	159 (72.9)	Ref
	Tertile 1	1803 (11.3)	23 (10.6)	1.15 (0.73, 1.83)
	Tertile 2	1825 (11.4)	18 (8.3)	0.9 (0.54, 1.49)
	Tertile 3	1660 (10.4)	18 (8.3)	1 (0.6, 1.66)
Dicamba	Never use	14415 (46.8)	156 (47)	Ref
	Tertile 1	5407 (17.5)	54 (16.3)	0.86 (0.61, 1.22)
	Tertile 2	5621 (18.2)	53 (16)	0.84 (0.59, 1.19)
	Tertile 3	5368 (17.4)	69 (20.8)	1.23 (0.88, 1.71)
EPTC	Never use	24585 (79.2)	279 (83)	Ref
	Tertile 1	2149 (6.9)	21 (6.3)	0.85 (0.54, 1.35)
	Tertile 2	2182 (7)	15 (4.5)	0.6 (0.35, 1.03)
	Tertile 3	2116 (6.8)	21 (6.3)	0.94 (0.59, 1.5)
Glyphosate	Never use	7709 (23.1)	95 (24.7)	Ref
	Tertile 1	8396 (25.1)	106 (27.6)	1.08 (0.81, 1.44)
	Tertile 2	8738 (26.2)	98 (25.5)	0.99 (0.73, 1.34)
	Tertile 3	8545 (25.6)	85 (22.1)	0.93 (0.67, 1.28)
Imazethapyr	Never use	16671 (54.5)	195 (59.1)	Ref
	Tertile 1	4730 (15.4)	49 (14.8)	0.96 (0.67, 1.36)
	Tertile 2	4620 (15.1)	42 (12.7)	0.89 (0.62, 1.29)
	Tertile 3	4594 (15)	44 (13.3)	1.05 (0.73, 1.53)
Metolachlor	Never use	16056 (52)	195 (58.4)	Ref
	Tertile 1	4970 (16.1)	45 (13.5)	0.73 (0.52, 1.03)
	Tertile 2	5057 (16.4)	42 (12.6)	0.7 (0.49, 1)
	Tertile 3	4770 (15.5)	52 (15.6)	0.98 (0.7, 1.36)
Paraquat	Never use	15305 (84.1)	232 (83.2)	Ref
	Tertile 1	961 (5.3)	15 (5.4)	1 (0.59, 1.71)

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	Tertile 2	973 (5.3)	21 (7.5)	1.4 (0.87, 2.24)
	Tertile 3	962 (5.3)	11 (3.9)	0.74 (0.39, 1.39)
Pendimethalin	Never use	10014 (62.2)	151 (67.4)	Ref
	Tertile 1	2078 (12.9)	30 (13.4)	1.1 (0.73, 1.66)
	Tertile 2	2064 (12.8)	27 (12.1)	1.12 (0.72, 1.72)
	Tertile 3	1954 (12.1)	16 (7.1)	0.81 (0.47, 1.4)
Petroleum	Never use	12420 (77.9)	184 (82.9)	Ref
	Tertile 1	1168 (7.3)	10 (4.5)	0.58 (0.3, 1.1)
	Tertile 2	1194 (7.5)	13 (5.9)	0.85 (0.48, 1.51)
	Tertile 3	1158 (7.3)	15 (6.8)	0.93 (0.54, 1.59)
Trifluralin	Never use	14086 (45.7)	137 (41.6)	Ref
	Tertile 1	5481 (17.8)	69 (21)	1.27 (0.92, 1.75)
	Tertile 2	5745 (18.6)	52 (15.8)	0.93 (0.65, 1.34)
	Tertile 3	5498 (17.8)	71 (21.6)	1.38 (0.98, 1.93)
2,4-D	Never use	6722 (21.6)	58 (17.1)	Ref
	Tertile 1	7680 (24.7)	78 (22.9)	1.13 (0.79, 1.62)
	Tertile 2	8428 (27.1)	97 (28.5)	1.12 (0.78, 1.61)
	Tertile 3	8294 (26.6)	107 (31.5)	1.05 (0.73, 1.52)
2,4,5 T	Never use	13132 (81.1)	171 (72.2)	Ref
	Tertile 1	1034 (6.4)	22 (9.3)	1.1 (0.68, 1.75)
	Tertile 2	1045 (6.5)	21 (8.9)	1.06 (0.66, 1.71)
	Tertile 3	973 (6)	23 (9.7)	1.26 (0.79, 2.01)
2,4,5 T P	Never use	15731 (94.9)	228 (95)	Ref
	≤ Median	429 (2.6)	5 (2.1)	0.59 (0.24, 1.46)
	> Median	408 (2.5)	7 (2.9)	0.87 (0.4, 1.89)
Atrazine	Never use	8359 (26.2)	89 (25.4)	Ref
	Tertile 1	7622 (23.9)	87 (24.8)	1.07 (0.77, 1.49)
	Tertile 2	8102 (25.4)	84 (23.9)	0.89 (0.63, 1.25)
	Tertile 3	7829 (24.5)	91 (25.9)	0.97 (0.69, 1.37)
Cyanazine	Never use	17558 (56.5)	189 (55.6)	Ref
	Tertile 1	4497 (14.5)	43 (12.6)	0.81 (0.56, 1.16)
	Tertile 2	4631 (14.9)	53 (15.6)	0.95 (0.68, 1.33)
	Tertile 3	4399 (14.2)	55 (16.2)	1.15 (0.82, 1.61)
Metribuzin	Never use	9363 (59.5)	136 (61.8)	Ref
	Tertile 1	2123 (13.5)	33 (15)	1.14 (0.75, 1.73)
	Tertile 2	2167 (13.8)	24 (10.9)	0.83 (0.52, 1.33)
	Tertile 3	2089 (13.3)	27 (12.3)	0.97 (0.62, 1.53)

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; OR,Odds Ratio

[a]OR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide)

Supplemental Table 6: Ever-use of pesticide reported at enrollment and PD risk in all participants using inverse probability weights

Pesticide	HR (95% CI)
Organochlorine insecticide	
Aldrin	0.90 (0.66, 1.23)
Chlordane	1.08 (0.83, 1.40)
Dieldrin	0.83 (0.57, 1.21)
DDT	0.82 (0.63, 1.08)
Heptachlor	1.06 (0.77, 1.45)
Toxaphene	0.79 (0.58, 1.08)
Lindane	0.92 (0.70, 1.20)
Carbamate insecticide	
Aldicarb	1.10 (0.70, 1.71)
Carbaryl	1.14 (0.90, 1.44)
Carbofuran	0.96 (0.75, 1.21)
Organophosphate insecticide	
Chlorpyrifos	0.89 (0.71, 1.10)
Coumaphos	1.05 (0.74, 1.49)
Diazinon	0.72 (0.56, 0.93)
Dichlorvos	1.15 (0.84, 1.56)
Fonofos	0.91 (0.70, 1.19)
Malathion	1.05 (0.80, 1.38)
Parathion	0.98 (0.74, 1.31)
Phorate ($\leq$ 63y)	1.30 (0.84, 2.00)
> 63y	0.72 (0.53, 0.98)
Terbufos	1.30 (1.02, 1.67)
Permethrin insecticide	
Permethrin (Crops)	1.00 (0.70, 1.43)
Permethrin (Animals)	1.10 (0.79, 1.54)
Fumigant	
Carbon disulfide/Carbon tetrachloride	1.03 (0.70, 1.53)
Aluminum phosphide	1.11 (0.67, 1.85)
Ethylene dibromide	0.37 (0.15, 0.90)
Methyl bromide	0.86 (0.58, 1.27)
Fungicide	
Benomyl (overall)	0.82 (0.51, 1.31)
($\leq$ 63y)	0.37 (0.13, 1.08)
> 63y	0.97 (0.58, 1.62)
Captan	0.88 (0.61, 1.28)
Chlorothalonil	0.96 (0.60, 1.54)
Maneb ($\leq$ 63y)	1.35 (0.63, 2.91)
> 63y	0.71 (0.42, 1.18)
Metalaxyl	0.85 (0.61, 1.18)
Herbicide	
Alachlor	1.16 (0.89, 1.50)
Butylate ($\leq$ 63y)	1.23 (0.81, 1.88)
> 63y	0.88 (0.64, 1.20)
Chlorimuron	1.03 (0.78, 1.36)
Dicamba	0.96 (0.73, 1.27)
EPTC	0.83 (0.60, 1.14)
Glyphosate	1.15 (0.89, 1.48)

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Imazethapyr	1.05 (0.80, 1.39)
Metolachlor	0.77 (0.60, 0.99)
Paraquat	1.19 (0.92, 1.55)
Pendimethalin	1.11 (0.86, 1.43)
Petroleum	0.97 (0.76, 1.23)
Trifluralin	1.32 (0.99, 1.77)
2,4-D	1.08 (0.80, 1.47)
2,4,5-T	1.61 (1.22, 2.12)
2,4,5-TP	0.38 (0.24, 0.62)
Atrazine	1.08 (0.81, 1.44)
Cyanazine	0.87 (0.66, 1.14)
Metribuzin	0.86 (0.65, 1.13)

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; OR,Odds Ratio
[a]HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide)

Supplemental table 7: Ever-use of pesticide reported through Phase 2 and PD risk in applicators (n=37,284)

Pesticide	No PD (n (%))	PD (n (%))	HR (95% CI)[a]
Organochlorine insecticide			
Aldrin	6311 (19.6)	96 (31.1)	0.91 (0.67, 1.23)
Chlordane	8556 (26.2)	119 (37.9)	1.03 (0.8, 1.33)
Dieldrin	2333 (7.2)	37 (12)	0.86 (0.59, 1.26)
DDT	8238 (25.2)	139 (44.3)	0.9 (0.7, 1.16)
Heptachlor	5291 (16.4)	87 (28.2)	1.09 (0.79, 1.49)
Toxaphene	5456 (16.6)	65 (20.6)	0.82 (0.62, 1.08)
Lindane	6733 (20.4)	73 (23.3)	0.94 (0.72, 1.23)
Carbamate insecticide			
Aldicarb	3747 (11.5)	27 (8.7)	0.92 (0.6, 1.41)
Carbaryl	19211 (58.2)	199 (64)	1.11 (0.85, 1.43)
Carbofuran	9795 (29.4)	115 (36.6)	1.08 (0.86, 1.36)
Organophosphate insecticide			
Chlorpyrifos	16197 (45)	142 (39.1)	0.90 (0.73, 1.11)
Coumaphos	3059 (9.3)	32 (10.5)	0.98 (0.68, 1.42)
Diazinon	11287 (34.2)	99 (31.8)	0.74 (0.56, 0.96)
Dichlorvos	3781 (11.4)	42 (13.7)	1.07 (0.77, 1.49)
Fonofos	7655 (22.8)	73 (23.2)	0.94 (0.71, 1.23)
Malathion	25236 (73.7)	260 (78.3)	1.05 (0.81, 1.37)
Parathion	5354 (16.3)	62 (19.8)	0.97 (0.73, 1.29)
Phorate	11251 (35.1)	115 (39)	0.97 (0.75, 1.24)
Terbufos	13922 (41.4)	146 (46.3)	1.28 (1.01, 1.62)
Permethrin insecticide			
Permethrin (Crops)	5198 (15.7)	38 (12.5)	0.96 (0.67, 1.36)
Permethrin (Animals)	5331 (15.9)	38 (12.3)	0.98 (0.69, 1.38)
Fumigant			
Carbon disulfide/Carbon tetrachloride	1922 (5.8)	29 (9.2)	1.01 (0.68, 1.5)
Aluminum phosphide	1714 (5.2)	17 (5.4)	1.11 (0.68, 1.82)
Ethylene dibromide	1253 (3.8)	5 (1.6)	0.34 (0.14, 0.82)
Methyl bromide	5299 (15.9)	47 (14.6)	0.82 (0.55, 1.21)
Fungicide			
Benomyl	3173 (9.9)	27 (8.9)	0.76 (0.47, 1.23)
Captan	4417 (13.3)	39 (12.6)	0.96 (0.68, 1.36)
Chlorothalonil	2740 (8.3)	23 (7.3)	1.05 (0.66, 1.67)
Maneb	3230 (9.8)	32 (10.3)	1.01 (0.64, 1.6)
Metalaxyl	8068 (24.2)	71 (22)	0.96 (0.70, 1.31)
Herbicide			
Alachlor	18743 (55.5)	192 (60.6)	1.11 (0.88, 1.39)
Butylate	11040 (33.5)	110 (35.4)	1.06 (0.82, 1.38)
Chlorimuron Ethyl	13088 (39.5)	106 (33.5)	0.99 (0.78, 1.26)
Dicamba	18455 (56.3)	171 (56.4)	1.03 (0.78, 1.38)

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EPTC	6882 (20.8)	53 (17.5)	0.85 (0.63, 1.16)
Glyphosate	31157 (85.5)	303 (82.8)	1.01 (0.75, 1.36)
Imazethapyr	15573 (47.5)	133 (43.9)	1.03 (0.78, 1.35)
Metolachlor	17568 (51.8)	136 (43.7)	0.80 (0.63, 1.02)
Paraquat	8306 (25)	85 (26.5)	1.03 (0.79, 1.34)
Pendimethalin	16680 (49.8)	145 (45.5)	1.00 (0.80, 1.26)
Petroleum	16338 (49.7)	155 (49.4)	0.99 (0.79, 1.24)
Trifluralin	18038 (56.1)	185 (62.1)	1.38 (1.04, 1.83)
2,4-D	29186 (80.7)	294 (81.2)	0.95 (0.72, 1.27)
2,4,5-T	7273 (22.3)	117 (37.5)	1.52 (1.18, 1.97)
2,4,5-TP	3181 (9.8)	23 (7.4)	0.39 (0.25, 0.62)
Atrazine	27689 (76.5)	276 (75.8)	1.04 (0.80, 1.35)
Cyanazine	14657 (43.6)	137 (44.1)	0.96 (0.75, 1.24)
Metribuzin	15357 (48.3)	138 (47.3)	0.85 (0.64, 1.13)

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; HR, Hazard Ratio
[a]HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide)

Supplemental Table 8: Comparison between pesticide exposure information reported at the AHS enrollment questionnaire and at FAME among FAME participants – in overall sample and by cases and control status

| | AHS exposure status at enrollment | | | | | | | | | | |
| | Overall FAME sample[a] | | | FAME cases | | | | FAME controls | | | |
	Exposed n (%)	Unexposed n (%)	Missing	All cases n (%)	Exposed n (%)	Unexpos ed n (%)	Missing	All controls	Exposed n (%)	Unexposed n (%)	Missing
FAME exposure											
Aldrin											
Exposed	91 (72.8)	28 (10.4)	7 (15.6)	26 (28)	16 (76.2)	8 (13.1)	2 (18.2)	100 (28.9)	75 (72.1)	20 (9.6)	5 (14.7)
Unexposed	34 (27.2)	241 (89.6)	38 (84.4)	67 (72)	5 (23.8)	53 (86.9)	9 (81.8)	246 (71.1)	29 (27.9)	188 (90.4)	29 (85.3)
DDT											
Exposed	130 (77.4)	65 (27.2)	16 (44.4)	47 (47)	28 (75.7)	17 (31.5)	2 (22.2)	164 (47.8)	102 (77.9)	48 (25.9)	14 (51.9)
Unexposed	38 (22.6)	174 (72.8)	20 (55.6)	53 (53)	9 (24.3)	37 (68.5)	7 (77.8)	179 (52.2)	29 (22.1)	137 (74.1)	13 (48.1)
Dieldrin											
Exposed	20 (38.5)	22 (7)	2 (4.2)	12 (13.6)	6 (60)	5 (7.2)	1 (11.1)	32 (9.8)	14 (33.3)	17 (6.9)	1 (2.6)
Unexposed	32 (61.5)	293 (93)	46 (95.8)	76 (86.4)	4 (40)	64 (92.8)	8 (88.9)	295 (90.2)	28 (66.7)	229 (93.1)	38 (97.4)
Parathion											
Exposed	8 (15.1)	5 (1.4)	3 (6.3)	6 (6)	3 (27.3)	3 (3.8)	0 (0)	10 (2.8)	5 (11.9)	2 (0.7)	3 (8.1)
Unexposed	45 (84.9)	346 (98.6)	45 (93.8)	94 (94)	8 (72.7)	75 (96.2)	11 (100)	342 (97.2)	37 (88.1)	271 (99.3)	34 (91.9)
Permethrin											
Exposed	19 (36.5)	35 (9.6)	3 (9.4)	16 (16.2)	3 (37.5)	11 (13.4)	2 (22.2)	41 (11.7)	16 (36.4)	24 (8.5)	1 (4.3)
Unexposed	33 (63.5)	330 (90.4)	29 (90.6)	83 (83.8)	5 (62.5)	71 (86.6)	7 (77.8)	309 (88.3)	28 (63.6)	259 (91.5)	22 (95.7)
Benomyl											
Exposed	11 (32.4)	10 (2.7)	1 (2.4)	7 (7.1)	4 (44.4)	3 (3.7)	0 (0)	15 (4.3)	7 (28)	7 (2.4)	1 (3)
Unexposed	23 (67.6)	365 (97.3)	41 (97.6)	92 (92.9)	5 (55.6)	78 (96.3)	9 (100)	337 (95.7)	18 (72)	287 (97.6)	32 (97)
Paraquat											
Exposed	41 (54.7)	25 (7.5)	6 (16.7)	23 (23.7)	10 (58.8)	11 (15.5)	2 (22.2)	49 (14.1)	31 (53.4)	14 (5.3)	4 (14.8)
Unexposed	34 (45.3)	308 (92.5)	30 (83.3)	74 (76.3)	7 (41.2)	60 (84.5)	7 (77.8)	298 (85.9)	27 (46.6)	248 (94.7)	23 (85.2)
2,4-D											

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Exposed	287 (92)	40 (30.1)	2 (25)	76 (73.8)	67 (94.4)	8 (28.6)	1 (25)	253 (72.3)	220 (91.3)	32 (30.5)	1 (25)
Unexposed	25 (8)	93 (69.9)	6 (75)	27 (26.2)	4 (5.6)	20 (71.4)	3 (75)	97 (27.7)	21 (8.7)	73 (69.5)	3 (75)
Trifluralin											
Exposed	151 (79.9)	36 (15.7)	5 (14.7)	46 (45.1)	42 (89.4)	3 (6.7)	1 (10)	146 (41.7)	109 (76.8)	33 (17.9)	4 (16.7)
Unexposed	38 (20.1)	193 (84.3)	29 (85.3)	56 (54.9)	5 (10.6)	42 (93.3)	9 (90)	204 (58.3)	33 (23.2)	151 (82.1)	20 (83.3)

Abbreviations: FAME, Farming and Movement Evaluation Study

Note: FAME asked exposure occurring prior to a reference date (cases: age at Parkinson's disease diagnosis and controls: median age of Parkinson's disease diagnosis for cases within the corresponding age-, sex, and state-specific stratum) whereas AHS enrollment asked ever-use of these pesticides

[a]FAME participants whose information on FAME exposure were excluded.

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